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FOREWORD

ALAN ROSS, M.D.

Consulting Editor

In all medical matters, and perhaps especially in Pædiatrics, the North American continent is unique in the free exchange of ideas and people across international borders. As a result, attitudes towards the investigation of disease, medical education, social problems and growth and development really show remarkable uniformity. Fundamentally, there is agreement on the direction in which Pædiatrics should move and the goals that eventually must be attained.

If it be true that geography in general and climate in particular determine to some extent the interests of medical men, perhaps this influence can be detected in this Canadian number of *Pediatric Clinics of North America*. Although most of the papers are review articles emphasizing recent advances to which the particular authors have made some contribution, it is appreciated that hardly is the ink dry before new light is shed on almost any problem. As the literature swells in volume and expands into fields that tend to diverge, the review article takes on the vital rôle of establishing communication between these fields.

For this reason it has seemed profitable to present in this volume a review of certain areas of pædiatric interest which are at present the concern of those working in the northern part of this continent.

REDUCTION IN NEONATAL MORTALITY

The Present and the Future

HARRY MEDOVY, M.D.

J. NIXON BRIGGS, M.D.

Has neonatal mortality reached the irreducible minimum?

Most physicians interested in problems of the newborn infant and his survival agree that this "irreducible minimum" has not been reached. Many are optimistic that recent progress and research at present under way give promise that a further significant drop in our present neonatal and infant mortality rate may not be too far away.

It is the purpose of this review to suggest (1) that even now, with knowledge at present available, our neonatal mortality rate should be lower than it is; (2) that concentration on prevention of neonatal mortality, especially in full-term babies, would be very rewarding; (3) that research now in progress is likely to bring about a notable reduction in both premature and neonatal deaths in the future.

THE PRESENT

The neonatal death rate according to the latest available figures for the following countries is as follows:

Norway and Sweden	13 per 1000 live births
New Zealand	14 per 1000 live births
England and Wales	17 per 1000 live births
U.S.A.	19 per 1000 live births
Canada	19 per 1000 live births

Vital Statistics, Dominion Bureau of Statistics, Canada, 1955.

Aided by a Dominion-Provincial Grant No. 606–7–19 for a study of Perinatal Mortality in Winnipeg Hospitals.[22, 23]

When one considers that in 1921 the corresponding rate for Canada stood at 43 per 1000, the extent of progress is obvious.

In every country a concerted effort to reduce neonatal mortality rates is always followed by a rapid initial drop followed by a slower fall as the "irreducible minimum" is reached (see Fig. 1). The last few years have witnessed little or no fall in mortality rate in the first few days of life. In the main this is due to the high death rate of premature infants, especially in the first 48 hours of life, and the inclusion in neonatal mortality rates of infants who live but a few minutes after birth.

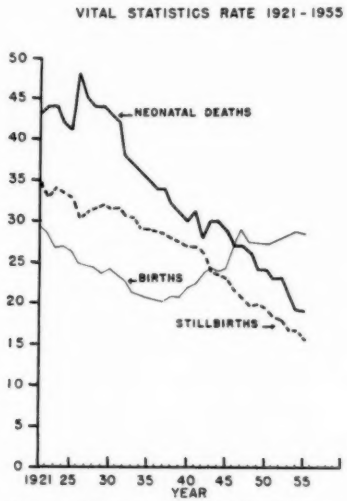

Fig. 1. Neonatal deaths and stillbirths per 1000 live births, and birth rate per 1000 population. (From Vital Statistics, Dominion Bureau of Statistics, Canada, 1955. [Statisque de L'Etat Civil Bureau Federal de la Statistique, 1955.])

The premature infant accounts for 50 to 75 per cent of our neonatal mortality rate.[4, 5, 6, 7, 15] This figure will not show any appreciable change until the obstetrician discovers why perfectly normal pregnancies terminate prematurely. Fundamental advances in our knowledge of the physiology of the premature infant's respiratory vascular and absorptive mechanisms must also be made. Until this occurs, no physician can claim any special technique which will reduce further the loss from hyaline membrane disease, atelectasis and intraventricular hæmorrhage. Neither can he alter the immature state of organ development which is part of prematurity itself.

In those instances in which prematurity is associated with maternal toxæmia, placenta prævia or maternal infection, or is due to carefully

planned obstetrical intervention as in diabetes and erythroblastosis, some improvement in survival is occurring as the result of improved medical and obstetrical care.

Neonatal deaths, however, still occur in full-term infants. When these result from gross congenital malformation or serious complications of pregnancy, we can do little to prevent them. When, however, they occur because of inadequate pre-natal care or failure to anticipate or recognize neonatal infection or erythroblastosis, then admittedly our neonatal mortality rate is still higher than it should be.

TABLE 1. *Anatomical Causes of Death in Different Studies*

POST-MORTEM FINDINGS*	CHICAGO Areal %	NEW YORK Areal %	LONDON† Hospital %	WINNIPEG Hospital %
Abnormal pulmonary ventilation and diffusion	47.5	40.0	26.6	27.7
Malformations	13.5	19.0	15.0	14.4
Anoxia	4.2	5.0	5.0	13.8
Infection	10.0	5.0	12.2	12.6
Hæmolytic disease of newborn	—	10.5	3.2	6.6
Trauma	18.3	17.0	18.1	6.0
Miscellaneous	1.0	—	5.4	5.4
Inconclusive and unknown	—	4.0	—	7.8
Per cent prematures	79.1	54.2	71.8	68.0
Total deaths	10,000	955	221	160
Per cent of autopsies in the series as a whole	89.0	35.0	100.0	92.0

* All figures for anatomical cause of death quoted in these cases are from autopsies only.

† The London study was a pure autopsy study.

Table 1 shows some of the main anatomical causes of death in four different studies and also the incidence of prematurity in each study.

THE MATURE INFANT

If the hope for reduction of mortality in the premature infant is rather slim just now, does the same hold true for the mature infant? Have we gone as far as we can to ensure that he will survive? The New York Study[15] indicated that the chance of finding a preventable cause of death in the term baby as compared with the premature is as 1.4 to 1. Our experience indicates an even greater spread between the incidence of preventable deaths in the full-term and the premature infant.

In this connection a study on perinatal mortality (1954–1957) is being carried on in Winnipeg. During this time, in one of the two hospitals under study, there were 160 neonatal deaths. Of these, 148

TABLE 2. *Neonatal Mortality, Winnipeg Hospital, A. 1954–7*

Total neonatal deaths autopsied	148 (100.0%)
Premature deaths (under 2500 gm.)	99 (66.9%)
Mature infant deaths	49 (33.1%)
Preventable premature deaths	5 (5.1%)
Preventable mature deaths	14 (28.6%)

infants came to autopsy. The findings in these 148 cases appear in Table 2.

PREVENTABILITY

How many of these deaths were preventable? Of the 148 infant deaths, there were 14 preventable deaths among 49 mature infants and only five out of 99 in the premature group.

It might be well at this point to explain what we mean by "preventability" and how we arrive at a decision that an infant death should be classed as "preventable." We have used for assessment of preventability the classification of Kendall and Rose[14] (Table 3).

TABLE 3. *Assessment of Preventability of Infant Deaths*

A. Obstetric	I. Preventable	1. Inadequate pre-natal care
B. Pædiatric	II. Non-preventable	2. Family at fault
C. Combined (obstetric-pædiatric)	III. Unclassifiable	3. Physician, error in judgement
		4. Physican, error in technique
		5. Intercurrent disease
		6. Unavoidable disaster

The information concerning each neonatal death was reviewed in the following manner before preventability by this classification was assigned:

1. A careful record of antenatal course, labour and post-natal course was entered on a punch card.

2. All sections and autopsy material were reviewed by the same pathologists for each of the two hospitals concerned in our study. In these two hospitals there were some 7000 live births annually.

3. The pædiatrician, obstetrician and pathologist in charge of the study reviewed each case in the light of information so obtained.

4. Finally, when this information was correlated, each neonatal death was discussed at a combined obstetrical-pædiatric meeting with the Professor of Obstetrics as Chairman and the Pathologist in attendance. A decision was first made as to whether the death was related to antepartum or intrapartum causes or to factors in neonatal life. The cases were then labelled as obstetric, pædiatric, or, when it was not possible to separate the two, a combined obstetric-pædiatric classification was assigned. Next a decision was reached as to preventa-

bility. Culpability was not the issue. Could the baby have survived had a reasonable application been made of available knowledge? If so, the case was classified as preventable by vote of all those present. The area in which preventability could have been achieved was next designated.

The following cases illustrate the method of assigning preventability and of focusing attention on the way death might have been avoided.

CASE I. A male infant weighing 3374 gm. was born to a Para O, gravida I, after 40 weeks' gestation with a normal antenatal course. The onset of labour was spontaneous. The first stage lasted 15 hours and 25 minutes. When the second stage commenced, the head rotated from a right occipito-anterior position to an occipito-posterior position. A difficult extraction then followed, with the forceps misapplied.

At birth the infant appeared well, but became collapsed and pale. He was scored at 60 seconds as Apgar 7. Intracranial hæmorrhage was diagnosed, and an intravenous transfusion of 50 ml. of whole blood was given, but the child died after 15 hours.

The post-mortem findings were bilateral tentorial tear and massive hæmorrhage.

The assessment was Obstetric, Preventable, Physician, error in technique (of delivery); code, A.I.4.

CASE II. A female infant weighing 3615 gm. was born to a Para O, gravida I, after 40 weeks' gestation. Labour lasted 18 hours. The membranes ruptured at the onset of the second stage.

The Apgar rating at 60 seconds was 6. The infant's respirations were shallow, and it had a poor sucking reflex. At 21 hours of age she was pale and icteric (bilirubin was 11.4 mg., indirect). Coombs' test was negative. The infant later became cyanotic, with sighing respirations at 28 hours. The child died at 49 hours.

Treatment with Digoxin, 0.02 mg., commenced at 28 hours, and with Ilotycin, 40 mg., at 38 hours.

The clinical diagnosis by the physician was cardiac failure.

The post-mortem findings were septicæmia, bronchopneumonia and pancarditis. All cultures were negative.

The assessment was Pædiatric, Preventable, Physician, error in judgement; code, B.I.3. (The diagnosis was in error. Sepsis should have been suspected. The treatment and investigation should have been undertaken with this in mind.)

CASE III. A female infant weighing 4536 gm. was born to a Para VI, gravida VIII. The mother was an extremely obese, prediabetic woman who attended her obstetrician only 3 times and refused to follow the advice given by him or his medical consultants. When she was admitted in labour at 40 weeks, she was pre-eclamptic, her blood pressure was 193/128, and the membranes had been ruptured for 30 hours. There was vertex presentation. Labour lasted 3 hours and 13 minutes.

The infant was scored as Apgar 1. Thick meconium was removed from the pharynx and larynx. The child died 2 minutes after birth.

The clinical diagnosis was anoxia, with aspiration of amniotic fluid and meconium.

The post-mortem findings were anoxia, with definite inhalation of amniotic fluid and meconium.

The assessment was Obstetric, Preventable, Family at fault (inadequate antenatal attendance on the part of the mother); code, A.1.2.

CASE IV. A male infant weighing 1029 gm. was born to a woman aged 39, Para IV, gravida VI. There had been one previous stillbirth at 28 weeks and one previous miscarriage. The present pregnancy was uneventful at 28 weeks' gestation. The membranes ruptured spontaneously. After 2 days, because labour had not commenced, artificial surgical induction was performed. Labour ensued, and the infant was delivered by breech extraction after 4 hours and 30 minutes.

At birth the infant was rated Apgar 4. It was limp, with poor respiratory effort,

and was resuscitated by the Krieselman resuscitator. The child improved, its heart rate rose from 60 to 100, but the respirations continued to be laboured, and there was considerable retraction of the intercostal spaces. Chloromycetin, 50 mg. intramuscularly, and crystalline penicillin, 100,000 units intramuscularly, were given. The child was nursed in oxygen at 35 per cent. Despite these measures, death occurred at 6 hours.

The clinical diagnosis was (1) hyaline membrane, (2) prematurity.

The post-mortem finding was extensive hyaline membrane formation in the lungs.

During the discussion it was considered that nothing was gained in inducing labour in this case at 28 weeks. It was felt that possibly, had this woman been left, she might have carried the infant for several weeks more and have delivered a larger infant better able to survive such risks as hyaline membrane or infection. It was recognized that the risks of a neonatal loss were high in view of the pregnancy record and early rupture of the membranes.

The assessment was Obstetric, Preventable, Physician, error in judgement; code, A.I.3.

We believe that cases I, II and III were all preventable deaths, while case IV is felt to be a preventable death had ideal circumstances obtained.

A review and classification of preventability of the deaths by our obstetric-pædiatric group soon showed that some deaths were preventable only if ideal circumstances obtained. We have often noted during discussion on any particular case that the physicians, anxious to serve the cause of better obstetrics and pædiatrics, tend to emphasize their failures even in cases in which the circumstances were such as to make survival of the newborn infant well nigh impossible. To classify such cases as preventable would therefore be unrealistic. We have modified Kendall and Rose's classification as follows:

1. *Practical Preventability*
   When the death should not have occurred had present knowledge been correctly applied (see cases I, II, III).
2. *Academic Preventability*
   When it might have been possible to prevent the death if an unlikely combination of ideal conditions had existed at the same time (see case IV).

Out of the 148 neonatal deaths with adequate autopsies in one of the hospitals under review, 19 cases were classified as preventable (Table 4).

Thus 10 deaths of the 49 term babies were classed as "practical preventable deaths," while only two of the 99 premature deaths could be so regarded. It is obvious that a concentration of attention on preventable full-term deaths would be most rewarding.

TABLE 4. *Preventable Causes of Death*

	CASES	GESTATION WEEKS	WEIGHT GM.	TOTAL	
Practical	Mature	39–45	2750–6776	10	12
	Premature	32–33	1531–1855	2	
Academic	Mature	36–40	2693–6002	4	7
	Premature	28–37	1087–2485	3	

PROGRAMME FOR PREVENTABILITY

A review of our data on factors of preventability leads us to make the following suggestions to lessen the number of needless deaths of full-term babies as well as of prematures.

1. INCREASED FACILITIES FOR PRENATAL CARE. Improve and increase facilities for prenatal care, especially among those patients most likely to neglect this important aspect of obstetrical care. There must be no economic barrier to reasonably frequent attendance. There should be some obligation of voluntary agencies to help solve any transportation or home care problems which might prevent regular maternal attendance.

This is one of the most fruitful areas in which to save newborn lives. In spite of the efforts of public health workers, nurses and physicians, too many women, especially those in the lower socio-economic groups, do not take the trouble to consult the obstetrician until they are actually in labour. The obstetrician loses the opportunity of preventing, correcting or modifying maternal complications which may lead to death in the newborn period.

TABLE 5. *Apgar Rating*

SIGN	0	1	2
Heart rate	Absent	Slow, below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Colour	Blue, pale	Body pink, extremities blue	Completely pink

2. CONCENTRATION OF ATTENTION ON BABIES WHO ARE IN DIFFICULTIES AT BIRTH. In order to focus attention on newborn infants who are in trouble from the moment of birth, we have adopted the Apgar[2] method (Table 5) of assessing and recording the baby's condition at birth. The infant is given a score of 0, 1 or 2 on each of five clinical signs which are readily observed. The total score possible is 10.

Infants scoring 6 to 10 do not usually present any problem. Infants scoring 1 to 5 need careful supervision for at least 24 to 48 hours. Some will respond quickly and will be normal babies. Some will present problems during the nursery period, owing to intra-uterine infection, anoxia or congenital malformations. Some will be infants

of diabetic mothers. Some will be in difficulties due to prolonged or difficult, complicated deliveries. It is in the group of infants scoring below 6 that most neonatal deaths occur.

Infants with a low Apgar score should be kept under continuous and careful nursery and medical observation. It is our feeling that a recovery station similar to the one used in most modern operating room areas, and staffed around the clock by highly trained nursing personnel, and with all necessary emergency diagnostic and treatment facilities is desirable in every newborn nursery where 2000 or more babies are delivered each year. The pædiatric resident should have his office adjoining such a station.

3. Early Recognition of Infection. Most neonatal infections are acquired *in utero*. A few originate in the postnatal period. Recognition may be difficult, but must be prompt if there is to be any hope of survival. There must be a high index of suspicion of infection in any nursery infant who is listless, feeds poorly, has some respiratory difficulty or has jaundice in the presence of some or all of the foregoing symptoms. Since differential diagnosis is difficult in the first two or three days of life, treatment should be started as soon as investigation is under way.

When conditions favour the development of intra-uterine infection, a program of prophylaxis is indicated, and treatment of the infant should start from the moment of birth (see p. 273).

4. Alert, Well-Trained Personnel. Fine buildings and shiny equipment do not necessarily mean that care is of the highest standard. We are dependent on the nursery staff for the recognition of early jaundice, pathological vomiting, pallor, cyanosis, purpura and a variety of other clinical states which cannot wait for the pædiatrician's daily ward round. Prompt treatment is often lifesaving. To achieve such a standard of skill and obtain a real sense of team-work, it is necessary to have a constant sharing of information between medical and nursery staffs. Regular review conferences including pædiatricians, obstetricians and nursing staff are valuable in maintaining interest and obtaining maximum cooperation.

5. Specialized Care of Conditions Which Commonly Cause Neonatal Deaths. Included in this group would be (*a*) respiratory distress syndrome, (*b*) congenital malformations, (*c*) erythroblastosis, (*d*) infections.

Many nurseries have well-organized special programmes for premature care. This has already resulted in an appreciable improvement in the premature survival rate to a point at which we must now await progress in basic research before we can advance any further.

As an example of the need for a specialized programme, when the mortality figures leave a good deal to be desired, one could cite the

example of erythroblastosis. In many communities the problem of erythroblastosis is handled in a haphazard manner. Case finding is inadequate, diagnosis is late or is not made at all, facilities for treatment by exchange transfusions are limited and scattered, and trained personnel for both diagnosis and treatment either non-existent or available to a limited degree. Problems of transportation to medical centres often increase the risk to the infant.

Most of these difficulties could be overcome as they are in Manitoba by a well-organized Blood Group Laboratory, operating with Dominion-Provincial (federal and state) assistance, housed in an obstetrical pavilion and affiliated with the University Department of Pædiatrics. The Laboratory serves as a combined research, treatment and case-finding organization. The records of all married women who are Rh negative (as obtained from pre-marital blood specimen) are kept there. Anticipatory guidance is given to obstetricians and pædiatricians as required. Admission is encouraged to one of three hospitals which maintain adequate diagnostic and treatment facilities always in readiness and with a trained "transfusion officer," a pædiatrician specially interested in erythroblastosis, available on 24-hour call at each hospital. Treatment is prompt, exchange transfusion often started less than an hour following birth, and the decision for transfusion or repeat transfusion is not influenced by any other consideration than the baby's clinical and laboratory status.

6. Maintenance of High Professional Standards. It seems hardly necessary to refer to the importance of insisting on professional competence by the medical staff of a hospital. To achieve this objective, there should be frequent reviews of perinatal morbidity and mortality and close co-operation between obstetrical, pædiatric, nursing and anæsthesiology departments.

THE FUTURE

After having achieved the "irreducible minimum" by application of knowledge we now possess, we can further reduce neonatal deaths only by the acquisition of new information through basic research. When satisfactory solutions are worked out for the following problems, a further important reduction in neonatal mortality is bound to result: (1) the respiratory distress syndrome, (2) the earlier recognition of fœtal distress, (3) the proper understanding of the problem of perinatal infection, (4) the prevention of prematurity, (5) the prevention of erythroblastosis due to Rh incompatibility.

THE RESPIRATORY DISTRESS SYNDROME

The demonstration by Craig and Gitlin,[12] using histochemical methods, that the material of which hyaline membrane is composed is fibrin has brought us a step nearer the solution of the problem of respiratory distress in the newborn infant. If we could reduce or climinate the deaths associated with hyaline membrane syndrome, we would bring about the sharpest reduction in neonatal death rates in

25 years. The present neonatal loss of prematures, babies of diabetic mothers and babies born by Cæsarean section is associated in many cases with respiratory distress accompanied by hyaline membrane formation. Twenty-five per cent of the premature deaths and 4 per cent of full-term infant deaths are associated with hyaline membrane disease.

Tentative approaches using fibrinolysins have so far proved ineffectual, and it may be that the developing pulmonary pathology associated with respiratory distress of prematures has a point of no return. Yet all of us have seen infants with moderately severe respiratory obstruction, apparently doomed to early neonatal death, recover completely. It is

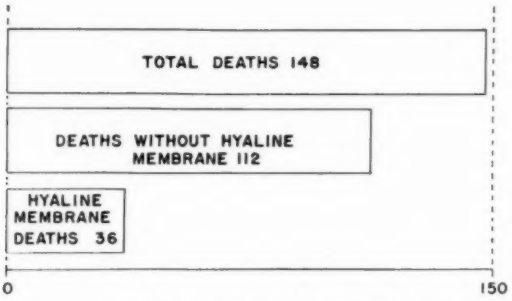

Fig. 2. Frequency of hyaline membrane formation in 148 autopsies.

true that in these cases we have no absolute proof that we are dealing with hyaline membrane formation, but on purely clinical and radiological grounds we cannot differentiate the survivors from those who eventually die. High humidity and ærosols have been of little or no help. We must, for the time being, base our hopes on the gradual unfolding of our knowledge of fibrinoid disease and the reduction of prematurity itself.

FŒTAL DISTRESS

Progress in the earlier recognition of fœtal distress would result in more live babies, and more live babies would live. How can the unborn infant communicate with us and let us know that his life-line is endangered, that the placenta which has nourished him so well is now running down like a defective battery and that unless we can rescue him in time he will have little or no chance to survive?

Fœtal distress is usually related to anoxia. This may have its origin in maternal anæmia, placental failure due to hæmorrhage, degenerative change, congenital malformation, or accident to the cord. Maternal

toxæmia, post-maturity diabetes and blood group incompatibilities may result in placental changes which impair its efficiency. The obstetrician recognizing the existence of conditions which may lead to fœtal anoxia is confronted with a difficult problem. His concern for the mother is complicated by anxiety about the chances for delivery of a living baby. Early intervention may benefit the mother, but may result in an immature infant who may not survive. Planned delay in the hope of delivering a more mature infant carries the risk of being confronted with a stillbirth or perinatal death resulting from prolonged anoxia and delayed recognition of fœtal distress.

In maternal toxæmia, delay may carry little advantage to the infant, who may be born showing evidence of intra-uterine starvation resulting from a scarred, infarcted, inefficient placenta.

The present methods of recognizing fœtal distress are crude and often inaccurate. The obstetrician must rely on his interpretation of changes in the fœtal heart sounds and on the presence of meconium in the amniotic fluid in a non-breech delivery. Both these findings are late evidences of fœtal hypoxia.

More direct measurements which might reveal the presence of fœtal distress fall into two categories: (1) the recording of activity of fœtal heart and brain; (2) measurements of placental function by biochemical assay.

Both methods are in the early stages of development, but enough has been done already to give promise that, with improvement in recording apparatus and with the collection of a sufficient number of cases, including controls, a real advance in our methods of recognizing early fœtal distress may not be too far off.

Fœtal Electrocardiography

Fœtal electrocardiography has been under study since 1906. Abdominal, vaginal and rectal leads have been used. Its use has been hampered until now because of the following difficulties: (1) alterations in the position of the fœtal heart in relation to the placing of electrodes on the maternal abdomen; (2) insulating effects of vernix, amniotic fluid and maternal abdominal wall; (3) insufficient sensitivity of recording apparatus commonly in use.

If the electrocardiogram tells us only the rate and rhythm of the fœtal heart, we are not really very much further ahead. Southern,[21] using especially constructed equipment (Sanborn), studied 96 patients by fœtal electrocardiography and in several instances was able to correlate oxygen saturation studies done on arterial cord blood at birth, two, four, six, eight and 10 minutes after birth (see Table 6). The series consisted of four groups: (1) 46 cases—normal late preg-

TABLE 6. *Pre-natal Electrocardiographic Variations of the Fœtus in (1) Normal Labour, (2) Fœtal Distress, and (3) Post-maturity, Correlated with the Levels of Arterial Oxygen Saturation in Cord Blood 2 Minutes after Birth*

AVERAGE ELECTROCARDIOGRAPHIC VARIATIONS, LEAD I	NORMAL VALUES	VALUES IN FŒTAL DISTRESS	VALUES IN POST-MATURITY
Arterial oxygen saturation per cent (2 minutes after birth)	47.5 ± 5.1	17.1 ± 4.1	30.1 ± 3.1
Fœtal heart rate (beats per minute)	127	102	118
P wave amplitude	0.05 mm.	1.10 mm.	0.71 mm.
P-R interval duration	0.06 sec.	0.12 sec.	0.09 sec.
QRS complex duration	0.02 sec.	0.06 sec.	0.05 sec.
S-T segment duration	0.09 sec.	0.12 sec.	0.11 sec.
T wave amplitude	0.03 mm.	Iso-electric or inverted in 35%	Iso-electric or inverted in 35%
Direction of T wave	Upright		

The numbers following the ± signs are the standard error of means.
From E. M. Southern; [11] reprinted with permission of the author.

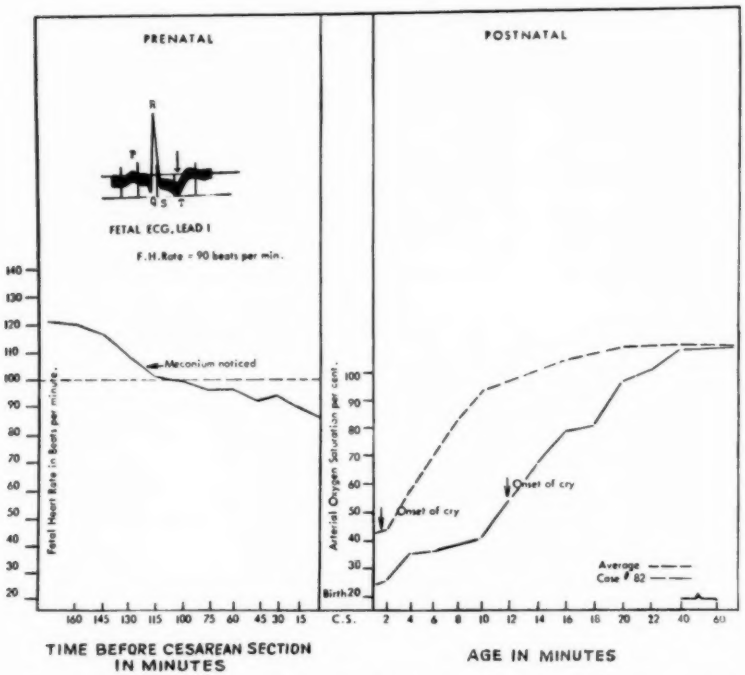

Fig. 3. Clinical and pre-natal electrocardiographic evidence of fetal distress related to recovery of the arterial oxygen saturation after birth. (E. M. Southern: *Am. J. Obst. & Gynec.*, Vol. 73, No. 2, p. 238, 1957. Reprinted with permission of the C. V. Mosby Company.)

nancy and labour; (2) 22 cases—suspected intra-uterine fœtal distress (fœtal heart rate less than 100, meconium and amniotic fluid in other than breech presentation); (3) 20 cases—maternal toxæmia and hypertension; (4) 8 cases—postmaturity.

Early changes suggestive of anoxia were depressed S-T segments and iso-electric or inverted T waves. Correlation was noted where clinical fœtal distress was evident and in some of the post-maturity cases (Fig. 3). Unfortunately, in the group which presents the greatest problem and in which most help of this kind is needed, namely, the group of maternal toxæmia, no such correlation was obtained.

Ahvenainen[1] showed a correlation between electrocardiographic findings in anoxic newborns and post-mortem evidence of coronary and myocardial pathology. The survivors showed a return to a normal electrocardiogram and recovery from anoxia.

Further advances in fœtal electrocardiography may be expected. With further refinements in apparatus, and observation of a sufficiently large number of cases, much useful information may be obtained which will guide the obstetrician in making decisions which may save babies now being lost.

Fœtal Encephalography

Fœtal encephalography has been used, but is still in the experimental stage. Both abdominal and vaginal leads have been used, and the tracings before delivery compare well with those taken from the infant's skull after delivery. The technique, however, requires further refinement before it can become a clinically useful test.

Tests of Placental Function

Placental dysfunction, which could compromise the survival of the newborn infant, can occasionally be assumed from the appearance of the placenta at birth. This is, of course, too late to be of help in preventing perinatal death. We must know before the baby is born that placental efficiency is impaired so that the fœtus may be rescued in time, without waiting for clinical signs of fœtal distress.

Work is proceeding in several centres, designed to clarify the mechanism of transfer of materials across the human placenta. Page[18] has grouped these mechanisms under three headings: (1) substances concerned with maintenance of biochemical hæmostasis. This concerns water and electrolytes. Transfer is at the rate of milligrams per second and is by rapid diffusion. (2) Substances concerned with fœtal nutrition—glucose, amino acids, vitamins. Transfer is at the rate of milligrams per minute and is by "carrier system" and by diffusion. (3) Sub-

stances of immunologic importance, e.g., plasma proteins, red blood cells. This is at the rate of milligrams per day, and is by leakage through large pores.

When, as a result of continuing research in this field, we reach the point at which objective measurements of placental transfer of various substances can be obtained with reasonable accuracy, we will be in a position to decide at what point to terminate labour in cases of maternal toxæmia, erythroblastosis, post-maturity and other pregnancy complications, in order to give the fœtus the best chance of survival.

PRE-NATALLY ACQUIRED NEONATAL INFECTION

The preventability of neonatal deaths due to infection is a most difficult problem to assess.[10] There are those who deny that infection is an important cause of stillbirth or neonatal death. This attitude may be the result of a combination of good fortune and a limited experience, but is more often due to misinformation which stems from a low autopsy rate. Clinical diagnosis of the cause of neonatal death is often grossly inaccurate. In the 1955 New York Academy of Medicine Perinatal Mortality Study, one of the conclusions reached was that, when a complete autopsy was performed, the death certificate diagnosis and the autopsy diagnosis agreed only 40 per cent of the time. Infection as the cause of neonatal death may be revealed only at the post-mortem table, and occasionally only by microscopic examination.

The following case report from the files of our Perinatal Mortality survey highlights the problem.

Case V. A woman aged 35, Para III, gravida IV, Rh positive, WR negative, had a history of a normal pregnancy. The previous pregnancies had been normal. The membranes ruptured on April 16th at 5 p.m. The onset of labour was on April 21st at 3 a.m. The amniotic fluid was murky and foul before delivery. No antibiotics had been given to the mother pre-natally. The first stage of labour lasted 5 hours, the second stage 5 minutes, and the third stage 20 minutes. Delivery was spontaneous.

The infant had laboured respirations at birth and had clinical and radiological evidence of pneumonia. The baby was given penicillin, streptomycin and Chloromycetin from the moment of birth. There was a temporary improvement followed by relapse, and the baby died on the fourth natal day.

The pathological report of the placenta was as follows: "Acute amnionitis and vasculitis of the cord." Culture of vaginal swabs showed "Micrococcus pyogenes and Streptococci."

At autopsy the baby was found to have acute bilateral pneumonia, early toxic necrosis of the liver, acute amnionitis and vasculitis of the placenta.

This, then, is an example of a case in which premature rupture of the membranes occurred, and in spite of a short delivery and treatment with antibiotics from the moment of birth the baby had evidence of intra-uterine pneumonia and generalized infection.

On the face of it, the prevention and treatment of infection in the newborn should be an easy matter. We know that under the following conditions newborn sepsis may be anticipated: (1) premature rupture of membranes (18 hours or more before delivery); (2) prolonged, difficult labour requiring manipulation and instrumentation beyond the use of low forceps; (3) artificial induction of labour; (4) murky amniotic fluid; (5) maternal illness and/or fever immediately preceding or during labour; (6) delivery outside of the hospital labour room under conditions less than ideal.

The recognition of the presence of infection of the newborn baby may be easy when fever and difficulty in breathing are present. It is more common for these findings to be absent, and we must rely on a high index of clinical suspicion of infection whenever listlessness and failure to thrive occur in a baby delivered under circumstances noted above. We know that infants with pre-natally acquired infection are stillborn or are likely to die within 48 hours after delivery. To be effective, treatment must commence at least from the moment of delivery. In spite of apparently adequate and aggressive prophylactic antibiotic routines practised in various centres, including our own, the impression prevails that at present our methods are inadequate to influence the outcome of perinatally acquired neonatal infection. Schaffer[20] in Baltimore feels that neonatal pneumonia may be treated successfully. His optimism is not shared by many other workers in this field.

There are many problems involved: (1) the conditions under which infection reaches and involves the fœtus; (2) the defence mechanisms of the newborn infant—(*a*) humoral, (*b*) cellular; (3) the efficacy of pre-natal treatment of the mother with antibiotics; (4) the treatment of neonatal infection by anticipation as compared with actual laboratory proof of infection at birth.

Routes of Infection

Maternal infection may reach the fœtus through one of two main routes: (1) *by transplacental passage of organisms from maternal to the fœtal blood stream.* The conditions under which this occurs are not known. It would appear that some organisms as they circulate in the blood in the intervillous space reach the fœtus, while others do not. Virulence and the presence of bacteria in large numbers may favour passage across the decidual barrier; phagocytosis and other mechanisms may prevent such a passage in other instances. In our present state of knowledge we must assume that the fœtus is infected if the mother has a bacteræmia.

2. *Via the fœtal membranes.* Infection may enter through the

maternal birth canal after rupture of the membranes. The evidence suggests that this occurs only after the onset of labour even when the membranes have been ruptured for a long time. The combination of premature rupture of membranes and prolonged or difficult labour renders infection of the fœtal membranes likely, and under these conditions we should assume that the newborn infant is infected. It is a little more difficult to explain the occurrence of such infection with intact fœtal membranes, and yet Blanc* finds that in 30 per cent of cases of neonatal sepsis, membranes are ruptured immediately preceding delivery.[3] It may be that near term the stretched-out membranes, relatively avascular and devitalized, form an ineffective barrier to infections from without.

Defence Mechanisms of the Fœtus

In recent years information has gradually accumulated about the defence mechanisms of the newborn infant, but much still remains unknown.

Humoral defence mechanisms are largely those determined by maternal transfer of passive antibody. This has been determined for diphtheria, Haemophilus influenza, tetanus and pertussis and is presumed for measles and mumps. The concentration of gamma globulin is the same in maternal and cord blood at birth. Non-specific humoral defence mechanisms are present in the newborn infant, as indicated by recent studies on the properdin system. Properdin is a protein of high molecular weight present in the plasma at all ages in equal concentration. The presence of magnesium and complement is required for its effective action. Its actual role in the protection of the fœtus against infection is not yet fully established, but it may well be one of the agencies which prevent generalized sepsis in the newborn infant even in the presence of pathogenic organisms in the nose and throat.

Cellular mechanisms which protect the infant have been the subject of recent investigation. The efficiency of phagocytosis in the newborn infant and the type of cellular response invoked by infection are important areas for fundamental research. According to Gluck and Silverman,[13] effective phagocytosis is directly proportional to birth weight. The term baby and the adult woman seem to possess equal powers of effective phagocytosis. In the premature this reaction is less effective. Addition of adult serum experimentally *in vitro* resulted in a significant increase in effective phagocytosis in premature infants. The phagocytosis-promoting factors in serum were identified as α_1, α_2 and β globulin fractions.

* W. A. Blanc: Personal communication.

Effect of Antibiotics Given to the Mother Pre-natally

Penicillin, streptomycin, chloramphenicol and tetracycline given to the mother will all reach the fœtus, but only penicillin is found in the amniotic fluid in therapeutic concentration. Charles[8] has suggested selective absorption of penicillin by the fœtal membranes. Eastman[9] has pointed out that in his series intensive antibiotic therapy given to the mother in the "latent period" between rupture of the membranes and the onset of labour is ineffective in preventing intra-partum infection or lowering perinatal mortality. In view of our ignorance of the type of organism involved in any given case, the giving of such therapy pre-natally to the mother can only be in the form of "shotgun" treatment and not in accord with scientfic indications.

Blanc[3] has attempted to determine the presence or absence of infection in the newborn at birth by seeking evidence of inflammation and microscopic examination of stained smears of amniotic shreds taken near the placental vessels and by examining aspirated stomach contents of the newborn for evidence of inflammatory cells.

Charles[8] tries to determine what organisms are involved in neonatal infection at birth by plating high vaginal swabs in cases in which the latent period between rupture of the membranes and the onset of labour is longer than 24 hours.

There is thus no agreement about the efficacy of maternal prophylaxis against intra-uterine infection of the fœtus. We do not know with certainty at present whether to treat, when to treat, and what antibiotic drugs to use.

The value of anticipatory treatment of the newly born infant from birth whenever the conditions are such as to favour infection is also not clear. There is a real need for a control study to determine the efficacy of various methods which have been suggested in the literature.

PREVENTION OF ERYTHROBLASTOSIS DUE TO Rh INCOMPATIBILITY

Dramatic success has accompanied the use of exchange transfusions in the management of erythroblastosis in infants. Largely because of this procedure, kernicterus due to blood group incompatibility has been almost eliminated. The use of premature induction of labour along with exchange transfusion in selected cases in which successive fœtal death has occurred has increased the number of newborn survivors. If we could assist the newborn in the conjugation of indirect bilirubin with glucuronic acid so that a soluble bilirubin not injurious to the brain cell would result, further reduction in neonatal mortality would result. Better still, it is possible that we may finally learn how to prevent erythroblastosis from developing altogether by preventing

the formation of specific antibody or by neutralizing it once it is formed. Exchange transfusion may then be reserved for failures in the prophylaxis of erythroblastosis.

SUMMARY

1. The irreducible minimum in neonatal deaths has not yet been reached.

2. Efficient application of available medical knowledge will reduce the present neonatal mortality rate, especially in full-term infants.

3. Further notable reduction is dependent on basic research designed to solve the problems of ætiology of prematurity, treatment of hyaline membrane disease, the prevention and/or treatment of intra-uterine infection of the fœtus and the prevention of fœtal erythroblastosis.

Associated in this project were Dr. A. J. DePape, Lecturer in Pædiatrics, University of Manitoba; Dr. James R. Mitchell, Demonstrator in Obstetrics and Gynæcology, University of Manitoba; and Dr. Georgina Hogg, Lecturer in Pathology, University of Manitoba.

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THE PLACE OF EARLY DELIVERY IN THE PREVENTION OF FOETAL DEATH FROM ERYTHROBLASTOSIS

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Nearly all babies born at term suffering from erythroblastosis of such degree as to require treatment can be treated successfully. Until such time as a method of prevention is found, the main problem that remains in this disease is stillbirth, which in some cases can be prevented by early termination of pregnancy. How can one know beforehand that a particular fœtus is threatened by death and must be born before its time if it is to live?

There is one group of fœtuses in whom the probability of death is high: the Rh-positive fœtuses of women who have already had one or more die of erythroblastosis *in utero*. Death of the fœtus that succeeds one that is stillborn is not inevitable, but the probability is so high that early delivery is justifiable; two fœtal deaths in a row make early delivery of the next fœtus almost mandatory, provided it lives to 32 weeks. Our own experience is that after a woman has had one fœtus dead of erythroblastosis the chances for the next Rh-positive fœtus are:

Stillbirth	75%
Born alive, but with extreme anæmia	15%
Born alive with readily treatable disease	10%

When a woman has had two stillbirths due to erythroblastosis, the chances for the next Rh-positive fœtus are:

Stillbirth	90%
Born alive, but with extreme anæmia	8%
Born alive with readily treatable disease	2%

With this background of experience we have in the past three years recommended early induction of labour when (1) a fœtal death has occurred in which the fœtus was proved by autopsy or by the fact that it was Rh-positive, Coombs-positive, to have suffered from erythroblastosis; (2) the father was homozygous Rh-positive; (3) the fœtus lived to 32 weeks.

Of fœtuses that die and have evidence of erythroblastosis, about half are hydropic and half not. While one may assume with reason that the former died of their erythroblastosis—though we do not understand the mechanism of hydrops, which may occasionally occur apart from blood group incompatibility—it is less certain that erythroblastosis killed the non-hydropic fœtuses. Yet that is the assumption we have felt we had to make, and have acted on it.

The zygosity of the husband raises a difficult point. Given a bad past pregnancy record and an almost hopeless prognosis for the birth of a living Rh-positive baby, is one justified in early induction of labour if the father is heterozygous? Generally speaking, one may expect a baby at 32 weeks to weigh around four pounds. In a good premature service the prognosis for a baby of such weight is good, though not 100 per cent. Furthermore, some of the babies we are discussing will be born by Cæsarean section; Cæsarean birth of a premature baby always carries a hazard for the baby.

We make the recommendations, but it falls to the obstetrician to carry the responsibility for the actual delivery; it is no light load. In our experience attempts at medical induction have been uniformly unsuccessful; the induction, if induction is decided upon, must be surgical; once a start has been made, there is no turning back, the obstetrician must go on until the baby is delivered. This requires of the obstetrician a nice assessment of the obstetrical situation, the lie of the fœtus, its size, the state of the cervix, the natural tendency of the woman to slow and difficult or rapid and easy labour. For we think delivery *per vaginam* is to be preferred in nearly every case to delivery by Cæsarean section; if active labour does not follow by 48 hours after surgical rupture of the membranes or withdrawal of the hind-waters, section may have to be done. But we ourselves are in no position to make sound recommendation for the best obstetrical handling of these patients.

The results of this policy of early delivery in closely selected cases have, on the whole, been gratifying; examples are set forth in the following case reports.

CASE I. Mrs. WEB, a patient of Dr. H. Lamontagne, Winnipeg, was blood group AB, rr. Her husband was blood group O, R_1R_2.*

* The genotypes are given in the British shorthand: R_1 = CDe; R_2 = cDE; r = cde. Antibodies were titrated by the albumin method and the saline method. The titre

In 1947 she had a normal pregnancy.

1948: Antibody titre was 0 at 13 weeks; A was 4 and S was O at 27 weeks; A 16 and S 0 at 32 weeks; A 32 and S 0 at 35 weeks. The fœtus was stillborn with hydrops at 35 weeks.

1950: Antibody titre was A 16 and S 0 throughout. The fœtus was stillborn with hydrops at 35 weeks.

1954: Antibody titre was A 16 and S 0. Labour was induced at 32 weeks, and a girl weighing 3 pounds 11 ounces was born. The cord hæmoglobin was 6.7; bilirubin, 5.2. Replacement transfusion was given at 3, 16, 26 and 60 hours. Development was normal at 30 months.

1956: Antibody titre was A 8 and S 0. Labour was induced at 32 weeks, and a boy weighing 4 pounds 15 ounces was delivered. Cord hæmoglobin was 6.9; bilirubin, 4.5. Replacement transfusion was given at 10 minutes and at 49 and 73 hours. Development was normal at 15 months.

Comment. It is hardly to be doubted that these babies would have died before 40 weeks. Mrs. WEB was fortunate to the extent that fœtal death, when it did occur, did so at approximately the same time in each pregnancy—34 or 35 weeks; it was on this basis that Dr. Lamontagne decided on induction at 32 weeks. With other women the time of foetal death may vary widely from one pregnancy to another and may all too often occur before 32 weeks, which we think the earliest time at which delivery can be recommended with hope of success.

Please observe the intensive treatment the first baby required: three replacement transfusions in the first 26 hours, and one additional when the bilirubin again rose close to 20 mg. If early induction is practised, you must be prepared to carry out this type of treatment if necessary. Mrs. WEB says she is going to have more children; we hope so, for there is some suggestion that antibody formation after eight years and five pregnancies is beginning to weaken; the titre was lower in the last pregnancy, the baby better grown and a little less ill than the preceding one. We think her prognosis is improving, though we cannot promise her a living baby.

Case II. Mrs. GLA, a patient of Dr. R. Tanner, Winnipeg, was blood group O, rr. Her husband's blood group was O, R_1R_1.

In 1947 she had a normal pregnancy.

A female child born in 1948 was admitted to the Hospital for Sick Children, Toronto, at 3 weeks of age because of persisting anæmia (7.7 gm.) in spite of small transfusions elsewhere. There was no history of jaundice. She responded to 4 transfusions of 75 ml. each.

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in albumin, indicated by the letter A, has the same meaning as the Canadian Red Cross Transfusion Service term 'late immune.' The titre in saline, indicated by the letter S, has the same meaning as 'early immune.' You must remember, however, that the titres we report are those for our laboratory; they cannot be transposed into the titres found in other laboratories. They are essentially the same as those recorded in the valuable series of articles by Diamond, Allen and their associates, but are higher than generally found in the Canadian Red Cross laboratories.

Hæmoglobin is recorded in grams per 100 ml. of blood; bilirubin in milligrams per 100 ml. of plasma.

1953: Antibody titre was A 32 and S 32 to 34 weeks, then A 64 and S 64. The baby was born at term. Cord hæmoglobin was 11.5; red blood cell count 2.7; reticulocytes 10.6; bilirubin 2. There was never more than a faint trace of jaundice; maximum bilirubin was 5. The hæmoglobin rose to 15.5 the day after birth and then fell rapidly to 4.9 on the ninth day. A single transfusion was given of 150 ml. of concentrated red cells.

1955: Antibody titre was A 32 and S 16 early in pregnancy. The titre fell steadily, but A more than S, to A 4 and S 8 at delivery at 35 weeks of a stillborn fœtus with hydrops.

1956: Antibody titre was A 16 and S 16 throughout. Labour was induced at 34 weeks, and a girl weighing 4 pounds 14 ounces was born. Cord hæmoglobin was 8.1; bilirubin 4.0. A single exchange transfusion at 2 hours raised the hæmoglobin to 15, but the hæmoglobin fell after the exchange to 4.9 at 4 weeks. A single transfusion of concentrated red cells was given. Development was normal at 9 months.

1957: Antibody titre was A 128 and S 64 early, falling to A 64 and S 64 at delivery at 34 weeks. The fœtus was alive at 33 weeks, but Dr. Tanner thought the uterus large for the age of the fœtus and that hydrops was developing. The baby was stillborn with hydrops.

Comment. There are several points of interest in this case: First, the falling A titre in the 1955 pregnancy with a lesser fall in the S titre, so that at the end of pregnancy the S titre stands higher than the A we think significant—a terminal rise or appearance of S antibody is generally a bad prognostic sign. Second, markedly higher titre in the 1957 pregnancy than in any previous one accompanied by disease of fatal degree—hydrops—at an earlier date than in the previous pregnancies, a date too early to allow delivery of a baby who could survive.

The babies in 1948 and 1953 followed the same course: minimal jaundice associated with rapid red blood cell destruction and probably complete, or almost complete, cessation of red cell production. We have observed this a few times as a family pattern of the disease. A fall in hæmoglobin after replacement transfusion is not uncommon, but a fall from 15 to 5 gm. in four weeks is. It is probable that this baby too was, during this time, producing no red cells of its own.

This woman has a poor chance of having a liveborn baby even as early as 32 weeks.

Case III. Mrs. HOU, a patient of Dr. O. Hjertaas of Prince Albert, was blood group O, rr. Her husband was O, R_1R_2.

In 1942 she had an abortion, and in 1943 a normal pregnancy.

1947–53: She had 6 stillbirths. Antibody titre was A 256 and S 16 in the first test following her second stillbirth in 1948. Since then the titre has stayed around A 128 and S 1, sometimes a little higher, sometimes a little lower.

1956: A girl weighing 5 pounds 6 ounces was delivered by Cæsarean section at about 35 weeks. Hæmoglobin was 5.2; reticulocytes 22; bilirubin 7.1. A single replacement transfusion was given.

Comment. This case is cited here because we have just said of Mrs. GLA (case II) that she has a poor chance of having a liveborn baby. She has, but the chance is poor, not zero, as case III illustrates. The first of Mrs. HOU's fœtuses to die did so at about seven months and

the rest at about six months; eventually she carried a baby to 35 weeks and, by delivery at that time, now has a living child.

We have the story of one woman, not in detail, who had some 30 pregnancies with one living child, her first. (That child's daughter has had several babies with erythroblastosis, but in them the disease has been mild.) According to the woman, many of these pregnancies ended in stillbirth, but some of the babies were born alive only to turn yellow and die in one, two or three days. The next is this sort of case from our own experience.

Case IV. Mrs. YAC, a patient of Drs. J. Johnson and D. B. Stewart of Vita, was blood group AB, rr. Her husband was A, R_1r.

In 1926 and again in 1929 she had a normal pregnancy, the infants being blood group A, R_1r.

In 1930 she had a child that died jaundiced at 3 days, and in 1931 a child that died jaundiced at one week.

In 1932 she had a twin pregnancy. One of the twins died 10 minutes after birth; the surviving twin is B, rr.

In 1934 she had a normal pregnancy, the child being blood group B, rr.

In 1937 she had a child that died jaundiced at one week.

In 1940 she had a normal pregnancy, the child being blood group B, rr.

In 1942 she had a stillbirth. The autopsy diagnosis was erythroblastosis.

In 1944 she had a normal pregnancy, the child being blood group A, rr.

1946: Antibody titre at 33 weeks was A 512 and S 0, and these values continued. Fœtal death occurred after 38 weeks. The blood group was A, R_1r.

1949: Antibody titre at 14 weeks was A 64, thereafter fluctuating, but generally downward, with no S antibody. A girl weighing 6 pounds 12 ounces was delivered at term; her blood group was B, R_1r. Cord hæmoglobin was 19.7; bilirubin 2.4. The baby had jaundice, but no other symptoms.

Comment. This type of case is exceptional and, in our experience, has usually been associated with more non-productive pregnancies than most women will face. There appears to be in some women a wearing out of the antibody mechanism, or at least a change in the lethal quality of the antibodies formed. The following two cases are examples of our commoner experience.

Case V. Mrs. VEN, a patient of Dr. R. Tanner, Winnipeg, was blood group A, rr. Her husband was O, rr.

In 1945 she had a normal pregnancy. The child was killed in an accident at the age of 7 years.

In 1948 she had a child that died jaundiced at 4 days.

In 1950 she had a child stillborn with hydrops.

1952: Antibody titre at 31 weeks was A 2 and S 0, rising to A 8 and S 0 at the time of delivery of a stillborn hydropic baby at 38½ weeks.

1955: Antibody titre was A 2 and S O throughout. A girl weighing 4 pounds 12 ounces was delivered by Cæsarean section at 34 weeks. Cord hæmoglobin was 6.0; bilirubin 5.4. Replacement transfusions were given at 3½, 30 and 50 hours. Development was normal at 15 months.

Comment. The antibody titre in this case was misleading; we have not seen such severe disease in any other case with an antibody of so

low titre. The fœtus in 1952 could probably have been saved by delivery at 34 to 36 weeks.

CASE VI. Mrs. DEM, a patient of Dr. R. S. Harris of Virden and Dr. O. Schmidt of Winnipeg, was blood group A, rr. Her husband was B, R_1R_1.

In 1942 she had an abortion.

In 1943 she gave birth to a child with marked jaundice.

In 1944 she had a stillbirth.

In 1946 and again in 1947 she gave birth to children with marked jaundice.

In 1950 she had another stillbirth. She had received an Rh-positive transfusion.

In 1951 another child was stillborn.

Antibody titre on a first pregnancy test in 1954 was A 32 and S 2.

1955: Antibody titre was A 16 and S 2. Labour was induced at 34 weeks, and a girl weighing 4 pounds 4 ounces was born. Cord hæmoglobin was 5.6; bilirubin 5.8. Replacement transfusions were given at 2½, 96 and 120 hours. Development was normal at 9 months.

Comment. We do not know whether the stillbirth in 1944 was due to erythroblastosis; if so, the sequence after that is unusual. The baby born in 1955 would undoubtedly have died had it been allowed to go to term.

In some cases one is put to it to decide what advice to give, and one can be wrong. The following is an example in which recommendation of early induction led to the death of a baby which, had it been allowed to go to term, probably would have survived.

CASE VII. Mrs. KUN, a patient of Dr. J. Menzies of Morden and Dr. C. McInnes of Winnipeg, was blood group B, rr. Her husband was A, R_1R_1.

In 1949 she had a premature baby.

In 1950 she had an abortion.

In 1951 she had a normal pregnancy.

In 1952 she had a stillborn child at 37 weeks. Antibody titre after delivery was A 128 and S 32.

1955: Antibody titre was A 8 and S 8 throughout. Labour was induced at 35 weeks, and a boy weighing 6 pounds was born. Cord hæmoglobin was 11.8; bilirubin 4.5. Four replacement transfusions were given at 1½, 40, 64 and 110 hours.

1957: Antibody titre was A 8 and S 8 throughout. Labour was induced at 35 weeks, and a boy weighing 5 pounds 10 ounces was born. A replacement transfusion was given at one hour. The baby died the next day. At autopsy a hyaline membrane lesion was found.

Comment. The first induction was justified by the history, but the recommendation for the second induction may well be questioned. The degree of disease in the 1955 baby was not so severe as to make it probable that it would have died before term. One would have been justified in the 1957 pregnancy to wait for at least another two weeks, if not to term.

We have made use of induction under one other circumstance: namely, when there has been a sudden rise in antibody titre of some magnitude. The following is an example.

CASE VIII. Mrs. GRA, a patient of Dr. J. Mitchell, Winnipeg, was blood group A, rr. Her husband was O, R_2r.

She had been badly burned in 1940, when she was 6 years old, and had received 3 transfusions.

1956: Antibody titre at 17 weeks was A 1 and S 0; at 22 and 28 weeks A 2 and S O; at 37 weeks A 256 and S 1. Labour was induced at once, and a boy weighing 5 pounds 4 ounces was born. Cord hæmoglobin was 10.8; bilirubin 9.6. Four replacement transfusions were given. Development was normal at one year.

Comment. The least rise in titre upon which we would base a recommendation of induction with any confidence is 4 dilutions; e.g., from a titre of 4 to one of 64. The rise in this case between the twenty-eighth and thirty-seventh weeks was 7 dilutions. Though one cannot say for certain that the baby would have died before term, we think the induction was justified. The serum not only had a high content of bilirubin, indicating rapid red cell destruction and poor disposal of bilirubin, but also contained methæmalbumin in sufficient quantity to give it a brown color; this we think is evidence of rapid destruction, indeed. In the 76 minutes between birth and the start of the first transfusion the serum bilirubin rose 4 mg. per 100 ml.

Such, then, are our indications for early termination of pregnancy and examples of our resulting experience. Early induction is no panacaea for the troubles of those poor women who have had one or more babies stillborn due to erythroblastosis; perhaps one can promise half of them a baby who will survive and develop normally. Nor can we even yet answer fully the question we first asked: How can one know beforehand that a particular fœtus is threatened by death? In particular, we cannot predict the first stillbirth. We think it doubly important to be able to do this, for it is our experience that while a mother who has lost a living baby from the disease is likely to try again, one who has had a stillbirth is not. Detailed study of the antibody curve and of the mother's pregnancy record will lead to the right decision in some cases, but additional methods must be found. Examination of the pigments in the amniotic fluid holds some promise, but in our own brief experience with this method we have seen at least one sudden rise in antibody titre due, we think, to needling of the placenta, probably with escape of fœtal blood into the mother's circulation. It is possible that the fœtal electrocardiogram may be of use, but we know of no study applied to these fœtuses. We can only hope that further investigation and study will answer our question.

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CONTROL OF INFECTIONS OF NEWBORN INFANTS

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Infections of the newborn are common, sometimes serious, and not infrequently fatal. Much has been written on this matter, but there remain deficiencies in our knowledge regarding the causative organisms, host resistance, methods of spread, prevention and treatment of these infections.

In this article the problem will be introduced by asking a series of questions. These will be discussed, and such answers as are available from the author's experience or from the literature will be presented.

WHAT INFECTIONS OCCUR IN NEWBORN INFANTS?

The four organisms most commonly isolated from infections in newly-born are *Staphylococcus pyogenes, Streptococcus pyogenes, Escherichia coli* and *Candida albicans*. Among others isolated less frequently are enterococci, klebsiellae, *Pseudomonas pyocyanea,* the Proteus species, salmonellæ, shigellæ, *Neiseria gonorrhœæ,* and some viruses. *Staphylococcus pyogenes* is found characteristically in infections of superficial skin, deeper soft tissue, bone, conjunctiva, lung and bowel. *Streptococcus pyogenes* causes umbilical infections[5, 32] and septicæmia. *Escherichia coli* is a frequent cause of meningitis, pneumonia and septicæmia. *Candida albicans* may cause stomatitis, œsophagitis and a dermatitis characteristically situated on the skin of the diaper area and other moist regions.

HOW FREQUENT ARE INFECTIONS OF NEWBORN INFANTS?

Henderson[25] reported that among 8075 newborn infants observed over a two-year period the incidence of major bacterial infections was 4.3 per

1000 live births. If we include minor infections with the major group, the incidence of infection will be much higher. For example, Crosse and Mackintosh[11] reported that 10.5 per cent of 1336 babies born in hospital acquired infection in the first 10 days of life. In 1952, at the Vancouver General Hospital, 4.6 per cent of 4639 newborn babies[21] became infected. Because of the propensity of premature infants to infection, their inclusion in any series increases the morbidity rate.

A recent analysis was made of all types of major and minor infections occurring in the Premature Unit of the Vancouver General Hospital. In the 12-month period ending May 12, 1957, 362 babies were admitted. This includes 266 premature infants and 96 larger infants admitted

TABLE 7. *86 Infections in 76 Infants, Premature Nursery, Vancouver General Hospital (May 13, 1956–May 12, 1957—362 Infants Admitted)*

TYPE OF INFECTION	NUMBER
Candidiasis (oral and/or cutaneous)	46
Pneumonia	12
Conjunctivitis	11
Upper respiratory infection	4
Omphalitis	3
Pyoderma	2
Enteritis	2
Septicaemia	2
Meningitis	1
Lymphadenopathy (? infection)	1
P.U.O.	1
Infected cut-down wound	1
TOTAL	86

for special care. As shown in Table 7, 76 (21 per cent) of the 362 babies were found to have 86 infections during life or at autopsy.

Although most of the infections listed in Table 7 are minor, infection was the cause of death in six infants, and a contributory cause in three. The incidence of certain infections of the newborn is suggested by the following reports.

Henderson[25] reported a consecutive series of 8075 newborn infants. Pneumonia occurred in 14, pyelitis in seven, omphalitis in six, septicæmia in five, and meningitis in three. Boissard *el al.*[5] found *Streptococcus pyogenes* in swabs of the umbilicus from five of 20 infants. Langewisch[33] described an epidemic of group A type I streptococcal infection involving 28 of 84 babies (33.3 per cent) in a newborn nursery. Kozinn and Taschdjian[31, 56] recently searched for the presence of *Candida albicans* in 2175 babies. Eighty-three were intestinal carriers, 81 of whom had clinical candidiasis (oral or cutaneous); 75 were oral carriers of the organism, 73 of whom had oral or cutaneous lesions. Umbilical swabs from 24 infants in two nurseries at the Vancouver General

Hospital were cultured recently. These infants were apparently well. Two other babies from these nurseries had been isolated during the previous three days with mild streptococcal pyoderma. Twenty-one of the 24 cultures grew *Streptococcus pyogenes* in pure culture or in combination with *Staphylococcus pyogenes*. Margileth[35] and Birdsong[3] recently described three cases of cytomegalic inclusion disease, thereby bringing the number reported in the literature up to 107. Smith[53] has described an epidemic of staphylococcal gastro-enteritis, in which 12 of 21 infants were affected. Donald,[13] in studying an epidemic of *H. influenzae* respiratory infection among premature infants, noted that 19 of 30 babies became ill and that positive nasopharyngeal cultures were obtained from 21. Hoffman[26] has drawn attention to an outbreak of infections due to *Pseudomonas pyocyaneus* (*Ps. aeroginosa*) in infants raised in mist (high humidity) atmosphere. Thirteen such infections occurred in a premature nursery during one year. Ravenholt, Laveck and Wysham[46, 47, 58] have reported the incidence of staphylococcal disease in maternity units in Seattle, Washington. Morbidity histories were obtained during the study of post-partum deaths from 714 mothers delivered in 15 Seattle hospitals in October, 1956. Average rates for suppurative illness during the first 30 days after delivery were 4.3 per cent for maternal mastitis, 1.0 per cent for infant mastitis, 18 per cent for infant pyoderma.

WHAT ARE THE CONSEQUENCES OF INFECTIONS OF THE NEWBORN?

Certain minor infections of the newborn seldom cause serious complications or death. They do not often spread to family contacts. Cutaneous and oral candidiasis are good examples of this type of infection. Yet the consequences of minor infection cannot be ignored. At considerable cost hospitals must provide additional nursing care and isolation facilities for the management of these babies. If the hospital stay for a baby is prolonged, there will be additional expense for the parents. Parental anxiety about the baby's welfare can result in a deterioration of good-will toward the hospital.

Major infections of the newborn can have important sequelae such as complications in the infants, spread of severe infection to the family, and increased mortality in the nursery population.

Complications

Staphylococcal infection provides the outstanding example of the severity of complications to infections in the newborn. Osteomyelitis, pneumonia, acute mastitis,[38] cerebral abscess[6] or chronic enteritis[9] may occur, and are characteristically difficult to treat.

Spread of Infection to the Family

Spread of serious staphylococcal infection to the family from newborn babies recently discharged from a nursery is a significant hazard. The baby may have a recognizable clinical infection or may be the carrier of a virulent pathogenic organism.[24, 29] There have been many epidemics of maternal mastitis, the infection having been spread from the contaminated suckling infant. Such a spread has also caused pyoderma in eczematous siblings, carbuncles on adults and enteritis in family members of all ages.

Kwantes[32] has emphasized the potential danger to family contacts from the presence of *Streptococcus pyogenes* in the umbilicus of newborn infants. He demonstrated that infants could carry this organism in the umbilicus for as long as eight weeks.

Mortality Due to Infection

Infection ranks high as a cause of neonatal deaths. Arey and Dent[1] studied 137 stillbirths and neonatal deaths. Infection was a primary cause in 16 per cent and a contributory cause in 27 per cent of 107 in whom an anatomic cause of death was discovered. Agnes MacGregor[34] reported that in 401 necropsies during 1949–53, death was caused by infection in 13.7 per cent. Nesbitt[43] reviewed 1043 perinatal deaths and found infection to be the primary cause of death in only 4.3 per cent. Expressing their results in a different manner, Crosse and Mackintosh[10] reviewed 18,301 live births in 1952, and found that death due to neonatal infection occurred at the rate of two per 1000 live births.

Pneumonia was the direct cause of death in 10 of the 107 neonatal autopsies reported by Arey and Dent.[1] Watson,[57] in a review of the literature, found that 0.5 to 2 per cent of neonatal deaths are due to purulent meningitis. During the epidemic reported by Ravenholt *et al.*[47] staphylococcal infection was established as the cause of death in 12 per cent of babies who died in one month (October, 1956).

DO INFECTIONS OF THE NEWBORN HAVE SPECIAL CHARACTERISTICS?

Infections of the newborn have certain special features. (1) The clinical picture may be misleading. (2) Resistance of premature infants to infection is less than it is among full-term infants, older children or adults. (3) Hospital nursery environment can contribute to the spread of infection. (4) The baby may share infection with its mother.

Clinical Picture of Infection

Sometimes infection of the newborn can be easily diagnosed. For example, oral or cutaneous candidiasis is readily recognized. Staphylo-

coccal pyoderma should not be misdiagnosed, but the inexperienced observer may confuse these infective lesions with those of toxic erythema of the newborn because of their similar appearance. The latter are sterile, and a direct smear of the whitish material from the lesion, prepared with Wright's stain, will show a predominance of eosinophils, instead of neutrophile polymorphonuclear white cells.

More serious infections, not confined to the superficial tissues, but more deeply invasive, such as pneumonia, meningitis or septicaemia, may be almost asymptomatic. A vague change in behaviour may be the only finding. There may be no fever; e.g., Smith[25] reports pyrexia in only 51 per cent of cases of neonatal septicaemia. The attention of an experienced nurse or doctor is attracted by the infant's listlessness or anorexia, or vomiting and diarrhoea or a disturbed respiratory pattern. Jaundice developed in 32 per cent of Smith's cases of septicaemia. Only about one-third of the babies with meningitis have early signs to suggest this diagnosis.

Thus it is possible for a newborn baby to sicken and die of an infection, having shown no more clinical disturbance than a vague lack of "being just right."

Resistance to Infection

Transplacental transfer of antibodies occurs. Levels of gamma globulin in mother's and full-term infant's blood are similar.[42] Premature infants are not so fortunate. Serum concentrations of total proteins, albumin and gamma globulin vary directly with the birth-weight of infants.[48] Antistreptolysin-O levels are usually higher in full-term newborn infant's blood than in the mother's blood.[12, 40] Staphylococcal antihemolysin levels were found by Murray and Calman[39] to be higher in cord blood than in mother's blood in the great majority of their cases. Premature and full-term infants respond to injections of diphtheria toxoid by producing significant levels of serum antibody, thus demonstrating their ability to form antibodies.[12]

Susceptibility of premature infants to infections can be partly explained by their low serum antibody levels. In addition, Gluck and Silverman[19] have shown that the phagocytic ability of the blood of prematures is less than that of full-term infants or adults.

Breast-fed infants probably do not receive significant amounts of antibodies from human colostrum. Nordbring[44] demonstarted that premature infants absorb small amounts (0.15 to 0.33 per cent) of the antibodies present in heterologous serum. When the same author[45] compared antistreptolysin and antistaphylolysin titres in sera and colostrum of 108 women, he found titres in colostrum to be lower than in sera

in the majority of cases, and also showed that the colostrum titres diminished considerably during the first three days.

At present it is not possible to define the rôle of the umbilicus in the development of neonatal infections, but past experience and recent evidence[5, 17, 30, 32] suggest that the umbilical wound is a potent reservoir of infection of the newborn. An excellent historical review of this subject is provided by Isabella Forshall.[17]

Hospital Nursery Environment

In North America most babies are delivered in hospital and spend their first few days of life in a nursery. There can be little doubt that this custom contributes to the spread of certain infections. There is much evidence that infection spreads between babies,[29] especially when the space provided for them is below the necessary minimum. Crowding in nurseries has the chief effect of allowing contamination of bedding by contiguity. Another ubiquitous problem in hospital nurseries is lack of staff. Harassed, over-busy nurses cannot practice a high standard of aseptic technique.

Shared Infections

Certain organisms may pass across the placenta, the fœtus sharing in its mother's infection. Examples of these intra-uterine infections are tuberculosis, syphilis, varicella, rubella and poliomyelitis.

Of vital importance is infection of the fœtus when chorio-amnionitis is present, perhaps while the membranes are still intact, but most often occurring after they have ruptured prematurely. The fœtus occasionally has the unenviable distinction of living in a sea of infected water.

Finally, the newborn infant can be infected during passage through a birth-canal contaminated with such organisms as *Neisseria gonorrhœæ* or *Candida albicans*.

WHAT MEASURES ARE AVAILABLE TO HELP CONTROL INFECTIONS OF NEWBORN INFANTS?

Control of infections of newborn infants is difficult, but good results can be expected when several techniques are used simultaneously. Early diagnosis is important, and infected infants must be treated and isolated promptly. Infection of the placental tissues should be suspected if the mother is febrile, if the membranes have ruptured prematurely, or if labour has been prolonged and difficult. The Public Health Authority should be notified when serious infection has occurred in a nursery. Sufficient space should be provided in nurseries so that over-

crowding is avoided. Nursery linen must be autoclaved. Premature or ill infants should be isolated from nursery air. Prophylactic measures for the infant's skin, umbilicus and eyes should be used. There must be enough nurses whose health is rigorously supervised. "Dangerous" nasal or throat carriers among the medical or nursing personnel must be excluded from the nursery. Under special circumstances to be discussed later, antibiotic prophylaxis may be instituted.

Early Diagnosis

A Pasteur pipette should be used when material is aspirated from pustules for culture. Organisms isolated by this method are not surface contaminants.

Taschdjian and Kozinn[56] have advocated that mouths of newborn infants be swabbed on their fourth day. The blastospore stage of *Candida albicans* can be identified on the stained smear one or two days before oral thrush develops. They recommend that prophylactic treatment be started when spores are found. Aqueous gentian violet, 0.5 per cent, painted in the mouth every 12 hours is effective.

The early diagnosis of urinary infection in the newborn infant depends on early examination of a urine specimen. Stansfeld[54] advocates that a urine cell count be done and suggests that counts of 50 pus cells per cubic millimeter or higher are significant.

Septicæmia is difficult to diagnose early because infants are often asymptomatic during the early stages of the infection. In the past we treated babies on suspicion, and took few blood cultures. Single blood cultures have been thought to be unreliable, and serial blood cultures have been impractical. However, Eitzman and Smith[14] have made an important contribution by showing that a significant bacteræmia is not frequently found in normal infants. Before taking the blood sample, the skin of the neck must be prepared by washing with pHisohex, 70 per cent alcohol and 2 per cent iodine consecutively. Using this technique, they conclude that "a blood culture from a newborn infant may be considered significant if the same micro-organism is found in pure culture on both broth flask and pour plate."

Isolation

Infants with pyoderma should be isolated without waiting for bacteriological reports. The skin, nose and blankets of infants with pyoderma are contaminated with *Staphylococcus pyogenes* significantly more often than are those of normal infants.[22] An infant so infected who remains in the nursery until the diagnosis is confirmed is a dangerous source of infection. However, Shaffer[49] has emphasized that isola-

tion of patients with cutaneous staphylococcal lesions is ineffective in controlling the occurrence of new cases, unless other measures of skin care are used coincidentally, because the presence of infants in the nursery with heavy nasal or umbilical colonization, but without manifest infection, would prevent control by isolation alone.

Langewisch[33] has said that isolation of infants infected with beta-hemolytic streptococci has little effect in limiting an epidemic, since new infants may become infected in the period necessary for incubation of the cultures. Infected infants should be isolated on discovery before culture reports are available.

The infant of a mother with an infection should be isolated. This is as important when the mother has acute upper respiratory disease, staphylococcal skin infection or diarrhœa as when she has a notifiable disease such as measles or poliomyelitis.

Management of Intra-uterine Infection

If the amniotic membranes have ruptured 24 hours or more before onset of labour, bacterial contamination of the amniotic fluid, fœtal membranes, placenta and fœtus may occur. Prolonged, difficult labour can have the same effect.

To help physicians determine when infants have acquired prenatal infection, McCredie Smith[37] has suggested that maternal pyrexia or fœtal tachycardia (over 160 per minute, sustained for at least 10 minutes) implies fœtal involvement. Blanc[4] reports that the presence of increased numbers of leucocytes in a smear of the placental surface at the maternal-fœtal junction is evidence of placentitis. He has also found large numbers of leucocytes in the gastric content of 80 per cent of newborn infants who subsequently had neonatal pneumonitis.

When intra-uterine infection threatens, antibiotics should be given to the mother. It is necessary to use two or three times the usual dose for at least 48 hours to achieve significant levels in the fœtal blood. McCredie Smith[37] recommends the use of streptomycin combined with oxytetracycline and reminds us that the organisms commonly causing perinatal death are insensitive to penicillin. Nesbitt[43] recommends penicillin and streptomycin or erythromycin with Gantrisin, but concludes that we "must take into consideration the significant possibility of intra-uterine pneumonia in the fetus despite adequate chemotherapy in the mother."

Infants have been observed with intra-uterine pneumonia in spite of apparently adequate administration of antibiotics to their mothers; therefore such infants should be given antibiotics from birth if the possibility of intra-uterine infection exists. Aqueous penicillin, 50,000 units intramuscularly every 12 hours, plus chloramphenicol, 50 to 100

mg. intramuscularly every 12 hours, appears to be the antibiotic regimen of choice.

Increase of the Infant's Resistance to Infection

Gluck[19] demonstrated that the poor phagocytic ability of premature infant's serum has been enhanced *in vitro* by addition of adult serum. There are no reports of therapeutic use of serum for this purpose, although some physicians have given blood serum from adults to premature infants as a supportive measure. Dancis and others,[12] giving high-protein milk feedings, failed to improve the ability of new-born infants to produce antitoxin after diphtheria toxoid injections. This suggests that high-protein feedings will not increase infants' production of antibodies.

Notification

When an outbreak of infection occurs in a nursery, the Public Health Authority should be notified and consulted. Shaffer[50] suggests that staphylococcal disease in infants under two months of age, and mastitis in nursing mothers, should be notifiable.

Nursery Environment

Hutchison[29] has shown that nursery conditions predispose to a higher incidence of neonatal staphylococcal infection than occurs if infants are cared for at their mother's bedside. He demonstrated that transmission of mother's nasal strains of *Staphylococcus pyogenes* to infants is infrequent. These results support the claim that "rooming-in" of infants with their mothers will prevent the spread of staphylococcal infection.

In a controlled study of the epidemiology of staphylococcal infections at the Vancouver General Hospital we failed to prove that there was a higher incidence of pyoderma among babies in more crowded nurseries than in less crowded nurseries. However, it is generally considered more difficult to prevent direct spread of infection between infants when minimum space requirements are not met. The provision of 30 square feet of floor space for each bassinet is mandatory.[27]

The manual of the American Academy of Pediatrics on Hospital Care of Newborn Infants[27] describes the proper care of nursery linen. It is especially important not to rely on laundering, but to autoclave all linen used in the nursery.

Clifford[7] has stated that "every infant should ideally be kept in his own completely enclosed and air-conditioned unit from admission to discharge." Premature and sick full-term infants can be provided with individual isolation in Isolettes. The use of this type of incubator is strongly recommended.

Care of the Skin

When hexachloraphene in detergent, soap or lotion is regularly applied to the skin of newborn infants, the incidence of staphylococcal pyoderma is reduced.[2,15,22,49] It is important to apply the protective film of hexachloraphene as soon after birth as possible. At the Vancouver General Hospital the infant gets a bath or inunction in the case-room immediately after delivery. This is repeated in the nursery every second day thereafter.

Our experience[22] and that of Shaffer[49] has been that there is an increased incidence of pyoderma when the skin is left dry. Inunction with ammoniated mercury ointment has not prevented the spread of staphylococcal infections. The routine use of antibiotic ointments is opposed because of the likelihood that organisms will develop resistance to the antibiotics.

Care of the Umbilicus

The care given to the umbilicus varies. In nurseries where "dry" skin care is the custom, the umbilical wound is often untreated. In many hospitals daily alcohol dressings are applied. Where regular pHisohex bathing has been done, as at the Vancouver General Hospital, the umbilicus has usually received no additional care. Recent reports that the umbilical wound is frequently heavily colonized with *Streptococcus pyogenes* and *Staphylococcus pyogenes* have stimulated interest in the care of this area. Jellard[30] applied triple dye* to the cord stump and to the skin 2.5 cm. around the cord at birth and daily. This reduced the nursery staphylococcal infection rate and the nose and skin colonization rate in infants. Contamination of the nursery air was similarly reduced.

Care of the Eyes

Neonatal infective conjunctivitis is a frequently unrecognized source of nursery infection. All infants with conjunctivitis, including those with a mild "sticky" eye, should be isolated. Swabs should be taken for culture and treatment instituted promptly. Drops containing neomycin, bacitracin or polymyxin B separately, or in combination, are recommended. One drop should be instilled in each eye every hour, if the infection is severe. Treatment may be given less frequently in milder cases. Sulfacetamide has also proved useful. Penicillin should be reserved for the treatment of gonorrhœal ophthalmia.

The prophylactic use of silver nitrate has greatly reduced the incidence of gonorrhœal eye infection, but not of staphylococcal conjunc-

* Brilliant green, 2.29 gm.; proflavine hemisulphate, 1.14 gm.; crystal violet, 2.29 gm.; water, 1000 ml.

tivitis. Prophylactic penicillin does not entirely prevent the occurrence of cases of staphylococcal eye disease,[23] although it does protect against gonorrhœal infection, and causes less chemical conjunctivitis than silver nitrate does.

Nursery Personnel

Persons employed in nurseries should be specially trained and should be suited for the work. They must not be so overworked, owing to staff shortage, that they lose their interest in good technique. It is important that their health be carefully supervised, so that they do not return to work having recently recovered from untreated or inadequately treated infections. Such persons may be "dangerous" carriers of streptococci for varying periods of time.[33] If a nurse is discovered to be a persistent nasal or throat carrier of a virulent strain of Staphylococcus that is predominant in the nasal cultures of the infants, she should be transferred.[2] Hare[24] has shown that some nasal carriers of staphylococci, having contaminated their skin and clothing, release organisms by friction, movement or hand-washing, even when wearing a sterile gown.

The nasal carrier state of nurses and patients has been influenced by local nasal instillation of antibiotics. Gould and Allan[20] considerably reduced nasal carriage of *Staphylococcus pyogenes* for three months after daily intra-nasal application of oxytetracycline cream for 10 days. Gillespie and Alder[18] treated noses of nurses and patients who were carriers of a virulent strain of *Staphylococcus pyogenes* with an ointment containing gramicidin and neomycin for one to four weeks and reduced the number of new carriers and infections in a children's hospital.

Nursery personnel must wash their hands before handling each infant. When pHisohex is used by nurses for hand-washing, it is not possible to recover *Staphylococcus pyogenes* from their hands.[22] However, it was found that this technique used alone, without concomitant pHisohex bathing of infants, did not prevent staphylococcal pyoderma. Murray and Colman[41] have reported favourably on an antiseptic hand-cream, Hibitane. The use of this cream by nurses and doctors after washing was accompanied by a decrease in the number of cases of staphylococcal infection on the wards and in the nurseries.

Antibiotics

Routine prophylactic use of antibiotics for newborn infants is unwise. Ready colonization of these babies by staphylococci makes the emergence of antibiotic-resistant strains of this organism especially dangerous. Caution is necessary in the use of drugs for premature infants. This

is illustrated by the experience of Silverman[51] that the prophylactic use of sulfisoxazole was apparently associated with higher mortality and higher incidence of kernicterus than occurred among premature infants not receiving this drug.

It may be necessary to use an antibiotic to control an epidemic of staphylococcal infection. Erythromycin has been used for this purpose by Shaffer.[49, 50] Langewisch[33] controlled an epidemic of streptococcal infection in a nursery by giving penicillin to all the infants as a prophylactic measure.

The majority opinion[8, 16, 55] remains against the use of antibiotics, prophylactically or for the simultaneous treatment of a large number of cases, unless the treated infants are removed from the nursery.

SUMMARY

Control of infections of newborn infants requires knowledge of the special problems involved. Signs and symptoms are often minimal, and diagnosis is difficult. The incidence of neonatal infections will be reduced only if many techniques are simultaneously used. Some of these measures are more important than others, but no one of them is sufficient alone.

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CLINICAL SYNDROMES CAUSED BY THE ADENOVIRUSES AND ECHO VIRUSES

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The investigation of virus diseases has progressed so rapidly in the past 10 years that the results of laboratory tests are no longer purely of academic interest, but can be of practical aid to the attending physician in the establishment of a diagnosis. It would appear to-day that virus diseases are increasing. While this increase may be relative, because of the control of bacterial infections, it is probably a genuine increase. Many new viruses have been isolated, and their rôle in clinical syndromes has been established.

Of considerable interest to pædiatricians are the adenoviruses, which cause respiratory illness, and the group of ECHO or "orphan" viruses. These two groups have been discovered only by the use of improved tissue culture techniques in the investigation of disease.

The chief stimulus to all this work on "new" viruses was the discovery by Enders, Weller and Robbins[11] that poliovirus causes degenerative changes in cultures of human embryonic tissues and that this change is prevented by specific immune serum. These changes, known

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as cytopathogenic changes, can be observed even under a low power of an ordinary light microscope. This simple, accurate and rapid method is now in general use for the routine laboratory diagnosis of poliomyelitis and some other virus infections.

New tissues and new techniques are constantly being tried in an effort to improve still further the usefulness of tissue culture methods. At present the most widely used cultures are epithelial cells derived either from monkey kidney or human amnion. Much effort is also being concentrated on the development of strains of cells that can be kept continuously propagated in the laboratory. HeLa cells derived from an epidermoid carcinoma of the cervix are widely used, particularly for the study of adenoviruses. Equipped with these varied tissue culture techniques, the modern virologist is in a good position to assist the clinician with prompt diagnosis. Speedy diagnosis was seldom possible in the days when fertile eggs and experimental animals had to be generally used for the isolation and identification of viruses.

ADENOVIRUSES

The adenoviruses cause catarrhal inflammation of the mucous membranes of the eye and upper respiratory tract. The original members of this group were recovered from adenoidal tissue and were called "adenoid degenerating" (AD) agents.[34] At this time other workers reported similar viruses and gave them various names such as respiratory illness (RI) virus[17] or acute respiratory disease (ARD) viruses.[13] The name 'adenoidal-pharyngeal-conjunctival' (APC) viruses[19] was originally suggested to cover the entire group, but this term has now been replaced by "adenoviruses."[10]

Sixteen distinct antigenic types of adenoviruses have now been identified.[33] These viruses share a common complement-fixing antigen, but can be differentiated by the virus neutralization test. Virus can be recovered from eye or throat washings in the early stage of the illness. It is present also in fæces and persists for longer periods. A rise in titre of neutralizing and complement-fixing antibodies can be demonstrated between acute and convalescent phase blood samples. Types 3, 4 and 7 adenoviruses have been most frequently associated with human illness.

Acute Respiratory Disease (ARD)

This is an acute infection of the respiratory tract characterized by cough and hoarseness. It is often associated with nasal obstruction, chest pain and constitutional symptoms. It appears to be primarily a disease of overcrowding, and is a particular problem in military recruits. As yet no epidemic of acute respiratory tract disease has been

reported in the civilian population. This fact has not been adequately explained. Hilleman and Werner,[17] investigating acute respiratory infections at Fort Leonard Wood, Missouri, during the winter of 1952–3, reported the isolation of an agent known as RI 67, which was later designated the prototype strain type 4 adenovirus. More recently Berge and his associates[4] have isolated adenovirus type 7 from throat washings in respiratory illnesses studied at Fort Ord, California. Types 4 and 7 appear to be the most common agents associated with acute respiratory disease.

Extensive serological surveys have been carried out in military recruits in England and in The Netherlands which support the findings in the United States.[36, 38] These viruses are probably widely disseminated.

Primary Atypical Pneumonia

It is now generally accepted that adenoviruses are the cause of a small proportion of illnesses presenting with the syndrome of primary atypical pneumonia.[14] These cases have been detected principally during an outbreak of ARD. Cold agglutinins and streptococcus MG agglutinins have not developed in convalescence.

Nonbacterial Exudative Pharyngitis

Nonbacterial exudative pharyngitis is a recognized entity in military medicine and occurs in association with ARD in military recruits. An outbreak occurred in the civilian population in Cleveland in 1954; type 3 adenovirus was the predominant agent.[15] This outbreak occurred mainly in children and was characterized by fever, headache and a severe pharyngitis with a thick yellow exudate. This syndrome is not common in civilian life.

Febrile Respiratory Infections

Adenoviruses, types 1, 2 and 5, have been most frequently recovered from the throat in association with upper respiratory tract infections in young children.[32] Most children develop antibodies to these types at a very early age. Although the types listed are those most frequently unmasked in adenoidal tissue, the exact relation between these findings has not yet been clarified.

Pharyngoconjunctival Fever

During the summer of 1954 an outbreak occurred among children in Washington, D.C., characterized by sore throat, fever and con-

junctivitis. In addition, cervical adenitis, headache and lassitude were prominent features. Bell and associates[3] investigated this outbreak and established type 3 adenovirus as the ætiological agent; spread was traced mainly to swimming pools. In 1955 a similar outbreak was studied in Toronto by Ormsby and Aitchison.[27] In the Toronto outbreak conjunctivitis occurred first in one eye, and spread to the other eye in a period of three to five days. Pharyngitis and fever were present. Generalized symptoms such as muscle pains were noted, and otitis media was a common complication. Type 7 adenovirus was isolated in this epidemic,[1] and again transmission was traced primarily to swimming pools with secondary spread in the homes of affected children.

Further outbreaks have been reported from Ohio and New Hampshire, and from England. In most cases so far described, type 3 adenovirus has been incriminated.

Conjunctivitis

Since 1954 sporadic cases of conjunctivitis have been investigated by one of us (H.L.O.), and adenoviruses have frequently been recovered in tissue cultures. In the winter of 1954–5 more than 20 adults with viral conjunctivitis were studied.[28] About half of these patients had corneal opacities. Virus was isolated from eye washings in seven cases, and four of these viruses were identified as adenovirus type 3. In 1955–6, 50 cases seen in Toronto Eye Clinics and The Hospital for Sick Children were investigated.[9] Thirty strains of adenovirus were isolated, and while types 3 and 7 were the predominant types, types 2 and 9 were also identified.

Evidence is accumulating to incriminate adenovirus type 8 as one cause of epidemic keratoconjunctivitis (EKC). Jawetz *et al.*[20] in California first isolated this type from conjunctival secretions of a merchant seaman with typical lesions. An epidemic of EKC occurred in the Ford Motor Plant in Windsor, Ontario, in 1951.[24] Convalescent sera from patients were later shown to contain antibodies to adenovirus type 8.[28]

The Use of Adenovirus Vaccines

Vaccines prepared against adenoviruses have been used with considerable success. Hilleman used a bivalent formalin-killed vaccine incorporating types 4 and 7, and reduced the number of hospitalized adenovirus cases by 98 per cent.[16] Huebner used a commercial trivalent vaccine containing types 3, 4 and 7. The use of this vaccine effected a reduction, estimated at 50 to 75 per cent, in the total of

febrile respiratory tract illnesses. The illnesses were associated with type 4 adenovirus infections.[2]

ECHO VIRUSES

As a "side-line" to the investigation of cases of poliomyelitis, viruses have been frequently isolated from the stools which cause cytopathogenic changes in tissue culture preparations, but which are not neutralized by antisera to the three types of poliomyelitis virus. These viruses are not usually pathogenic for suckling mice, and do not therefore qualify for inclusion in the Coxsackie group. They have been placed in a group known as the enteric cytopathogenic human orphan (ECHO) viruses.[7] This group now comprises 20 individual members, antigenically distinct.

The ætiological rôle of those members of the group which have been isolated only from stool is not yet clarified. The following criteria have been recommended by Huebner[18] as a guide to the ætiological significances of virus isolates:

1. The virus must be well established by animal or tissue culture passage in the laboratory.
2. The virus must originate in the human specimens under study, and this should be proved by repeated isolation. Latent virus in the experimental animal, cells or media must be excluded.
3. The agent should be shown to produce an active infection as revealed by an increase in serum antibodies.
4. A serious attempt should be made to determine its relationship, particularly on immunological grounds, to previously described agents.
5. The agent should be constantly associated with a well-defined and recognizable clinical entity.
6. Inoculation in human beings should reproduce a clinical syndrome consistent with the natural disease.
7. Carefully conceived epidemiological studies co-ordinating laboratory and clinical observations should finally establish the ætiological rôle of the virus in human disease.

Evidence has now accumulated that several of the ECHO viruses fulfil most of these recommendations, particularly in relation to the syndrome of aseptic meningitis.

Aseptic Meningitis Caused by ECHO Viruses*

It is now well established that only a small percentage of cases presenting with the clinical syndrome of aseptic meningitis are caused by polioviruses, contrary to views commonly held by North American

* See also page 313.

pædiatricians a few years ago. For example, in a series of 96 cases of aseptic meningitis in Toronto, Ontario, from 1947 to 1956, Rhodes and Beale[31] reported that only 19 per cent were caused by poliomyelitis virus, 24 per cent by Coxsackie B, and 11 per cent were caused by ECHO viruses. Ten different types of ECHO viruses have now been found associated with the syndrome of aseptic meningitis,[35] but, of these, types 4, 6 and 9 have been most frequently reported. Cases have presented the usual features of fever, headache, photophobia, stiffness of the neck, and muscular weakness.

The rôle of ECHO type 6 in causation of the aseptic meningitis syndrome has been well established. In the investigation of clinical poliomyelitis in Massachusetts in 1954, Kibrick[22] identified 58 per cent of strains isolated as ECHO type 6. Davis and Melnick,[8] in the evaluation of poliomyelitis vaccine in Connecticut in 1955, isolated 69 agents from non-paralytic cases. These isolates were made up of 41 per cent polioviruses, 23 per cent Coxsackie, and 36 per cent ECHO viruses, chiefly type 6.

Also in 1955, Karzon *et al.*,[21] investigating a localized outbreak of aseptic meningitis in Holland, New York, established ECHO type 6 as the infecting agent. Seven cases from this outbreak were hospitalized and presented with the typical signs and symptoms of aseptic meningitis. Fever lasted three to six days, meningeal irritation was present in all cases, and severe frontal headache was a constant complaint. Three patients had slight muscular weakness during the acute illness, but this was transient. The cerebrospinal fluids showed cell counts ranging from 32 to 231 cells per cubic millimeter, the majority being lymphocytes. From the children in hospital, virus of ECHO type 6 was isolated from seven stools and four throat washings. Thirteen healthy contacts and three non-hospitalized cases were also investigated, and two isolations were made in the former and one in the latter group. Rising antibody titres to ECHO 6 were demonstrated. Reviewing cases in Erie County, New York, in the same year, this group of workers[37] reported the isolation of ECHO type 6 from 68 per cent of 156 cases investigated. In eight out of 11 specimens, virus was recovered from the cerebrospinal fluid. This high percentage of isolations, combined with the recovery of virus from cerebrospinal fluid, and the rising antibody titres, constitutes acceptable evidence that ECHO type 6 causes aseptic meningitis.

ECHO virus type 4 was found associated with an epidemic of 'non-poliomyelitis-like' illness which occurred in Marshalltown, Iowa, in 1955.[6] Twenty-three strains recovered from 21 patients and two family contacts were identified as ECHO type 4. A rise in neutralizing antibodies was demonstrated. This investigation supported the observation that many minor illnesses occur concurrently with aseptic meningitis.

Since 1952 sporadic cases of aseptic meningitis in Toronto have been

associated with ECHO viruses.[31] In 1955 and 1957 ECHO type 6 was identified, but no significant outbreak due to this type has occurred. Echo type 9 was the predominant strain in the 1956 epidemic, which is described in the next section.

Aseptic Meningitis Associated with a Maculo-papular Rash

The clinical entity of aseptic meningitis associated with a rubelliform rash was probably first reported in 1946 in Sweden by Gabinus.[13] Since that time several isolated outbreaks have occurred. In 1956 extensive epidemics of this entity occurred in several European countries[5, 29] and in Canada. ECHO virus type 9 has been isolated in recent outbreaks.[12, 23]

In Toronto 115 children were admitted to The Hospital for Sick Children during the summer months of 1956, and pathological specimens were studied in our laboratories.[23] We understand that many more cases occurred in the city, but the mildness of the infection did not warrant admission to hospital.

The clinical picture in our hospitalized patients was chiefly one of aseptic meningitis.[23] A biphasic illness occurred in 43 per cent of cases. The chief features of the major phase were fever, headache, neck rigidity, vomiting and muscle pains. A rubelliform rash, finely maculopapular, appeared one or two days before the onset of the major illness. It covered the face, trunk and extremities and was observed on the palms and soles. The illness was of short duration and recovery was complete.

An unusually high cerebrospinal fluid cell count up to 2000 cells per cubic millimeter has been a constant finding in all recorded outbreaks.

The virus in the recent epidemics, although related to prototype ECHO type 9 virus by neutralization procedures, causes paralysis and death in suckling mice. Histologically, the lesions resemble those of Coxsackie group A, but no antigenic relationship has been found with any of the Coxsackie A viruses which produce cytopathic changes in tissue culture. A particular feature of the virus studies has been the frequent isolation of this virus strain from cerebrospinal fluid.

In Halifax, Nova Scotia, a small family outbreak in a relatively isolated community occurred in February and March, 1957.[12] The illness appears to have been restricted to one family, and enquiries revealed no current illness in school children or in the general population. Two cases had a distinctive rash, and ECHO virus type 9 was isolated from stool.

In the summer of 1957 we had an opportunity to investigate a localized outbreak in Thorold, Ontario. Three families were involved, and

these were closely related. In all, four children and two mothers were affected. The illness in the children was very mild, the main feature being a rubelliform rash. The mothers were more acutely ill, and one woman was admitted to hospital with meningitis. Virus was isolated from stool in five cases, and was found to be ECHO type 9.

In Toronto, during the seasonal occurrence of aseptic meningitis in 1957, some cases were associated with ECHO type 9 infection. A rubelliform rash was a prominent feature. Cases were sporadic, and no large outbreak was reported.

Boston Exanthem

In 1951 a widespread epidemic of an exanthem occurred in Boston, Massachusetts. The disease was mild, but had a high attack rate, especially among children. Fever, followed in one to two days by a pink maculo-papular rash involving the face, trunk and extremities, were the principal signs.[26] In adults frontal headache was characteristic, and the rash was less conspicuous. No meningeal signs were elicited. Cytopathogenic agents were isolated from the fæces of these cases.[25] Similar agents were isolated by Neva from patients in a smaller outbreak in Pittsburgh, Pennsylvania, in 1954. These isolates appear to be related to viruses recovered by Kibrick from cases of aseptic meningitis occurring in Boston in 1951.[22] Here, again, we have an example of antigenically identical strains giving rise to wide variation in clinical picture from mild exanthems to severe meningitis indistinguishable from non-paralytic poliomyelitis.

Diarrhœa

Investigations carried out in Cincinnati, Ohio, in 1955[30] on children admitted to hospital with diarrhœa, showed a high incidence of virus infections. The viruses isolated included type 1 poliovirus, Coxsackie A9, B1 and B2, ECHO viruses types 2, 8, 11 and 12, adenoviruses type 3, and five unclassified diarrhœal strains. Most of the patients from whom agents were isolated developed antibody shortly after their illness, suggesting that disease and infection were at least concurrent and possibly related.

"New" Viruses in Southern Ontario

Identification of 'new' viruses and correlation of laboratory studies with clinical investigation have been a particular interest in Toronto for over 10 years. During this period, infections with Coxsackie viruses, adenoviruses and ECHO viruses have frequently been described in

TABLE 8. *Identification of Certain "New" Viruses—Southern Ontario, 1950–1957*

YEAR	CLINICAL SYNDROME	PREDOMINANT STRAIN	OTHER STRAINS PREVALENT	REFERENCES
1950	Aseptic meningitis	Coxsackie B1	—	31
1951	Epidemic keratoconjunctivitis	Adenovirus type 8	—	28
	Aseptic meningitis	Coxsackie B2	—	31
1952	Aseptic meningitis	Coxsackie B4	ECHO (untyped)	31
1954	Aseptic meningitis	Coxsackie B2	ECHO (untyped)	31
1954–5	Sporadic conjunctivitis	Adenovirus type 3	Adenovirus type 8	28
1955	Aseptic meningitis	ECHO (untyped)	ECHO type 6 Coxsackie B2 and B5	31
	Pharyngoconjunctival fever	Adenovirus type 7	—	1
1955–6	Sporadic conjunctivitis	Adenoviruses types 3 and 7	Adenoviruses types 2 and 9	9
1956	Aseptic meningitis with rash	ECHO type 9	—	23
	Aseptic meningitis without rash	ECHO type 9	—	23
1957	Aseptic meningitis with rash	ECHO type 9	—	Unpublished
	Aseptic meningitis without rash	ECHO type 9	ECHO type 6 Coxsackie A9, B3, B5	Unpublished

Toronto and other parts of Southern Ontario. A summary of the principal viruses and the clinical syndromes associated with them is presented in Table 8.

SUMMARY

1. This paper reviews the principal clinical syndromes caused by the newly described adenoviruses and the ECHO viruses.

2. A general description of syndromes caused by adenoviruses is presented. It is concluded that they are the causal agents of acute

respiratory tract disease (ARD), pharyngoconjunctival (PC) fever, and some cases of epidemic keratoconjunctivitis (EKC).

3. It is concluded that several types of ECHO viruses, particularly types 4, 6 and 9, have been identified as the ætiological agents in seasonal outbreaks of aseptic meningitis.

4. A description of the newly recognized clinical entity aseptic meningitis with a rash, caused by ECHO virus type 9, is given.

5. This review has been prepared on the basis of a study of the above-mentioned syndromes over the past 10 years. During this period clinical entities caused by the following viruses have been identified in Toronto and other parts of Southern Ontario: Coxsackie types A9, B1, B2, B3, B4, B5; ECHO types 6 and 9; adenoviruses types 2, 3, 7, 8 and 9.

6. It is evident that a number of clinical syndromes in childhood are caused by Coxsackie viruses, ECHO viruses and adenoviruses. It seems likely that further study will reveal the increasing importance of these viruses as ætiological agents in disease.

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ASEPTIC MENINGITIS

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The purpose of this paper is to review the current status of aseptic meningitis and present a discussion of the problem chiefly from the standpoint of the physician who may encounter the condition in practice.

Aseptic meningitis, in reality, is not a specific entity, but rather a syndrome which, from an ætiological standpoint, may be caused by a great variety of agents both infectious and non-infectious.

HISTORICAL NOTE

The condition was first described by Wallgren in 1924 as a result of his observations of a number of outbreaks of this disease in various parts of Europe. It was implied in Wallgren's paper that the disease was a new and specific entity. Certainly the outbreaks described may well have been of a common ætiology because of the geographical localization. It is now apparent, however, as a result of information obtained by more recent laboratory diagnostic techniques, especially in the field of virus culture and isolation methods, that the syndrome may be induced by many agents, but is principally of viral origin.

The criteria for the diagnosis of aseptic meningitis as outlined by Wallgren in 1924 were as follows: (*a*) acute onset with meningeal symptoms; (*b*) cerebrospinal fluid, pleocytosis, predominantly mononuclear; (*c*) sterile cerebrospinal fluid; (*d*) comparatively short duration without secondary complications and with complete recovery; (*e*) absence of any indications of a para-meningeal ætiology such as otitis, sinusitis, trauma, and so on, or of such meningitogenic infections as mumps, poliomyelitis, epidemic encephalitis, leptospirosis, and so forth;

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(*f*) absence of epidemiological connections with the above-mentioned infectious diseases.

At the time Wallgren outlined the criteria for the diagnosis of aseptic meningitis, virus research was in its infancy, and the diagnosis was based on clinical and epidemiological grounds and a process of exclusion of the then known infections. Now it is possible, in many cases, to determine the specific ætiological agent, and, as Wallgren stated in 1951, he accepts the general opinion that aseptic meningitis represents a syndrome likely to be encountered in a number of different diseases. In the broad sense of the term and for practical purposes, any condition producing meningeal irritation and a cellular response in the cerebrospinal fluid, but bacteriologically sterile, might be considered under the broad classification of aseptic meningitis.

CLINICAL PICTURE

The clinical picture in aseptic meningitis may be as varied as the number of different causes. The more typical case, however, presents with a history of several days' indisposition characterized by drowsiness, headache which is usually frontal and may be severe, fever of 100° to 103° F., nausea, vomiting, and a variable degree of neck and back pain and stiffness. In addition, a significant number of cases are accompanied by abdominal pain, diarrhœa, generalized muscular aches and pains, and sore throat. Some cases have a definite prodromal phase followed by a two- or three-day period of relative well-being, this in turn followed by the major phase of the illness, a so-called dromedary type of illness, not infrequently observed in acute poliomyelitis. For the past few years we have been seeing aseptic meningitis in the Toronto area accompanied by a maculo-papular cutaneous eruption during the acute phase.

In the majority of cases of aseptic meningitis after the first few days of acute illness there is a steady general improvement in the patient's condition toward complete recovery over the following four to 10 days with no complications or sequelae.

On physical examination these patients show surprisingly little, aside from the stiffness of the neck and spinal muscles. There may be some pharyngeal injection with petechiæ or even ulceration. In some the maculo-papular cutaneous rash mentioned above is seen; however, no localizing neurological signs are present. The peripheral white blood cell count is normal or only slightly elevated with a relatively normal differential. The cerebrospinal fluid is under some increased pressure, and a pleocytosis of 30 to 3000 cells may be found, usually 50 to 300. These cells are mostly mononuclears, but early in the disease they may be predominantly polymorphonuclear, leading to the erroneous diag-

nosis of a purulent meningitis. The cerebrospinal fluid protein may be moderately elevated; however, the sugar and chloride are normal. As the name of the disease implies, blood and cerebrospinal fluid cultures are bacteriologically sterile.

ÆTIOLOGY

In 1955 Dr. Alex Steigman[10] prepared an excellent paper on this subject in *Pediatric Clinics of North America* and summarized the causes of aseptic meningitis in a comprehensive table. With his permission, this table is reproduced with a few additions made in the light of further virus research material published during the two years subsequent to the appearance of his paper (Table 9). From this table it is apparent that the syndrome of aseptic meningitis may be produced by a wide variety of agents. It is predominantly the infectious causes, however, with which we propose to deal in this outline. This is undoubtedly the most frequently encountered form of the disease and the one for which it is of some importance to have a rational concept and plan of management.

The chief infectious causes for the aseptic meningitis syndrome and simulating conditions have been summarized in Table 10 with clinical and laboratory aids to differentiation.

DISCUSSION OF DIFFERENTIAL DIAGNOSIS

It has been our experience at The Hospital for Sick Children that the most confusing problem, especially for the house physicians, is the differentiation of cases of aseptic meningitis from conditions which simulate this syndrome, namely, early *tuberculous meningitis* and early acute *purulent bacterial meningitis*. In both these conditions the cerebrospinal fluid, history and physical examination may closely simulate the aseptic meningitis syndrome. In most cases, however, the patient with aseptic meningitis does not appear as ill as the one suffering from an early acute purulent meningitis. The cerebrospinal fluid cell counts may be identical in the two conditions, but in the bacterial meningitis the sugar will be decreased in most cases, and within 24 hours the culture will reveal the causative organism. The peripheral white blood cell count will be elevated with a polymorphonuclear increase in most cases of purulent meningitis. If there is any reasonable doubt about the differential diagnosis, it has been our policy to treat the patient as having purulent meningitis for at least 24 hours until the results of the cerebrospinal fluid cultures are available and may contribute to a more definite diagnosis.

In tuberculous meningitis the history, intracutaneous tuberculin test,

TABLE 9. *Clinical Conditions Which May Induce the Aseptic Meningitis Syndrome (After A. J. Steigman*[10])

AGENT	DISEASE
I. Infectious:	
A. Viral:	
1. Established viral origin:	
a. Transmitted	
(1) Man to man:	
Poliomyelitis, mumps, herpes simplex, herpes zoster, Coxsackie B and A9, atypical pneumonia, infectious hepatitis, ECHO virus 4, 6, 9	
(2) Rodent to man:	
Lymphocytic choriomeningitis	
(3) Arthropod to man:	
Arthropod-borne encephalitides, including Eastern, Western and St. Louis	
2. Presumed viral origin:	Infectious mononucleosis, infectious lymphocytosis, cat scratch disease
B. Spirochætal:	
Leptospira icterohæmorrhagiæ, canicola, pomona, Treponema pallidum	Leptospirosis, syphilis
C. Yeast	E.g., torulosis
D. Protozoal	Toxoplasmosis
E. Helminthic	Trichinosis
F. Bacterial:	
1. M. tuberculosis	1. Very early meningitis
2. Bacteria causing purulent meningitis	2. Meningitis modified by partial suppression of organism by suboptimal antibiotic therapy
3. Bacteria leading indirectly to mechanical encephalopathy	3. Pertussis
II. Post-infectious	Measles, rubella, varicella, mumps, vaccinia, variola
III. Non-infectious:	
A. Meningeal irritation or reaction from neighbouring lesions	Sinus, mastoid, abscess, thrombosis, haematomas, infiltrates
B. Toxins and irritants:	
1. Systemic poisons	E.g., lead, arsenic, bacterial
2. Intrathecal injections	Sera, antibiotics, air, Lipiodol
C. Allergy:	
1. Medications	Serum sickness, including due to antibiotics
2. Prophylactic injections	Rabies, pertussis vaccine
3. Other allergens (?)	Seen rarely in association with urticaria and arthralgias

chest x-ray and reduced sugar and chloride in the cerebrospinal fluid plus the cerebrospinal fluid cultures later will clarify this differential diagnostic problem.

Suboptimally treated purulent meningitis may also simulate the

TABLE 10. *Diagnostic Aids in Common Types of Aseptic Meningitis and Simulating Infections*

TYPE OF MENINGITIS	CLINICAL DATA	LABORATORY AND CEREBROSPINAL FLUID DATA
A. Viral	1. Concurrent epidemic 2. Seasonal distribution	1. Virus isolation from stool or pharyngeal secretions
1. Non-paralytic poliomyelitis	3. Development lower motor neuron paresis 4. Reflex changes	2. Acute and convalescent sera for neutralization tests and antibody titre
2. Mumps (non-glandular)	1. Known exposure to case 2. Development of parotitis, pancreatitis, orchitis	1. Elevated serum amylase 2. Positive mumps complement fixation test on serum
3. Coxsackie B	1. Accompanying or following pleurodynia occasionally	1. Virus isolation from stool 2. Acute and convalescent sera for virus neutralization tests
4. Echo virus 4, 6, 9	1. Concurrent epidemic 2. Maculo-papular rash	1. Virus isolation from cerebrospinal fluid and stool 2. Acute and convalescent sera for virus neutralization tests
5. Specific viral encephalitis (Eastern, Western, Equine, St. Louis, etc.)	1. Geographic distribution 2. Reflex abnormalities, sensory disturbances	1. Neutralization and complement fixation tests on sera
6. Post-infectious encephalitis	1. History of measles, rubella, varicella, vaccinia, variola or recent exposure 2. Typical rash at time of illness or developing shortly after onset	
B. Non-viral (bacterial simulating aseptic meningitis)		
1. Tuberculous meningitis	1. History of exposure 2. Positive intracutaneous tuberculin test 3. Chest x-ray	Cerebrospinal fluid pellicle formation Reduced chloride and sugar Tubercle bacillus on smear and culture
2. Acute purulent meningitis	1. Early in course of disease 2. Modified by suboptimal anti-microbial therapy	Cerebrospinal fluid bacterial identification on smear and culture Reduced sugar
3. Leptospirosis	History of exposure to possible source; icterus, nephritis	Sera for agglutination and complement fixation tests.

aseptic meningitis syndrome, but in this condition the history, course and cerebrospinal fluid cultures will help clarify the diagnosis.

Leptospirosis is an extremely uncommon condition in this area; however, if evidence of icterus or nephritis develops during the course of an illness typical of aseptic meningitis, this diagnosis should be considered and the blood, urine and cerebrospinal fluid examined for leptospirosis in addition to agglutination tests on the patient's blood. As lepto-

spirosis may be anicteric, in some areas this condition may prove a difficult differential problem early in the course of the illness.

In most instances the aseptic meningitis syndrome appears to be of obvious viral origin, and in probably over 80 per cent of cases the chief viruses incriminated in North America are mumps, lymphocytic choriomeningitis, herpes simplex, poliomyelitis, Coxsackie B and ECHO virus 6, 9 and 4. I do not know of any published figures on the incidence of all these various types of viral aseptic meningitis. It is obvious that this figure must vary considerably, geographically and seasonally.

TABLE 11. *Virus Isolations from Cases of Aseptic Meningitis* (After Robert Ward)

YEAR	INVESTIGATOR	NUMBER OF CASES	ECHO	COXSACKIE	POLIOMYELITIS
1951	Enders	8	8		
	Enders	43	37 (all type 6)*	3 (B's)	3
	Smadel	17	13 (11 type 6)*	4 (B's)	
	Dalldorf	?	Outbreaks of type 6 in Troy and Buffalo "55"		
	Wenner	?	Outbreak of type 4		
	Habel	105	"Type 6 predom."	B's (24%) Occas. A9 (5%)	Type 1, 2 Rare 3 (33%)
1952	Rhodes	33	8	13 (B 4s)	3
1956	Karzon	24	Type 6		
	Davis and Melnick	24	Type 6		
	Rhodes		Type 9 with rash Also 4 and 6		

* All patients showed type 6 antibody rise.

Non-glandular mumps constitutes one large group of the aseptic meningitis syndrome, and this specific diagnosis must be considered in practically every case. History of exposure, concurrent epidemic, elevated blood serum amylase, abdominal pain, and orchitis in the older patient may be helpful diagnostic clues; however, in the absence of typical salivary gland involvement the most reliable specific diagnostic test is a positive mumps complement fixation test on the patient's serum.

Lymphocytic choriomeningitis is a relatively rare disease in most parts of North America, occurring usually in localized outbreaks among people exposed to or handling infected mice. It is therefore a hazard of laboratory personnel. The cerebrospinal fluid usually shows a decided pleocytosis, and the virus may be cultured from this source.

Herpes simplex is also a rare form of aseptic meningitis and can be diagnosed only in the absence of mucocutaneous lesions by isolation

of the virus from the cerebrospinal fluid or demonstrating a rise in titre of antibodies during convalescence.

Of all the viral causes of the aseptic meningitis syndrome, the most frequently encountered agents in this area appear to be similar to those reported in many parts of the United States. This group includes non-paralytic poliomyelitis, Coxsackie B and the various ECHO virus infections.

On a clinical basis we have found it impossible to differentiate these viral aseptic meningitides in most cases, and we are dependent on the virus laboratory to provide the definitive or specific diagnosis. I believe that this must be universally true, judging from the virus isolations from aseptic meningitis cases shown in Table 11, in which the patients all had similar histories and physical findings.

ASEPTIC MENINGITIS WITH RASH (A RECENTLY RECOGNIZED ENTITY)

An interesting illness has been appearing in the Toronto area during the past few years, occurring predominantly in the summer and fall months. It is characterized by a typical aseptic meningitis picture in children from infancy to 10 years of age; however, it is accompanied by a characteristic maculo-papular cutaneous eruption. This disease has been a relatively common condition in practice, and a number of cases have been admitted to The Hospital for Sick Children with various diagnoses and have received careful investigation, including virus studies. The rash has been present at some time during the course of the illness in as high as 60 per cent of some series of aseptic meningitis patients admitted to the Hospital. It has been observed to involve all parts of the body, but appears to have a predilection for the face and trunk. In some cases involvement of the palms of the hands and soles of the feet has been a notable feature. A few cases have had a petechial type of rash and were admitted as possible meningococcal infection; however, on further investigation and observation they were proved to be aseptic meningitis. The rash subsides over a period of five to 10 days with no scaling or desquamation. The rash is similar in most cases to that of rubella; however, occipital glandular enlargement has not been a prominent feature in these cases. ECHO 9 virus has been isolated from the stool and cerebrospinal fluid in a number of these cases by the virus laboratory under the direction of Dr. A. J. Rhodes.

It is interesting to note a report by Hennessen, Odenthal and Wunder of the Academy of Medicine, Düsseldorf, Germany, describing an epidemic of aseptic meningitis which occurred in northwest Europe in 1956. A virus was isolated from the sputa and fæces of patients with this disease; however, it was not classified further than

to report that it was not a strain of poliomyelitis. A number of these patients were reported to have transient rashes, a fact which fits closely the picture presented by the cases observed in the Toronto area.

Before a newly recognized agent can be said to be the ætiological agent of a disease, it must be shown to have a high correlation with the occurrence of the illness. Although some of the viruses isolated from stools of patients with aseptic meningitis have also been found in apparently normal members of the population, there have been sufficient isolations from the cases of aseptic meningitis to establish a firm ætiological relationship. The fact that the virus is recoverable from the cerebrospinal fluid in some of these cases is most convincing evidence to incriminate specific viruses in the aseptic meningitis syndrome.

The differential diagnosis of aseptic meningitis has been a confusing problem in many centres for a number of years. With the encouraging progress in virus isolation techniques and serological studies in conjunction with a more general awareness among physicians of the syndrome, many of these cases are now falling into their correct specific group entities and are being more accurately diagnosed.

It is apparent from these remarks that the problem of aseptic meningitis is a complex one and requires careful clinical and laboratory study to arrive at an accurate diagnosis. In this part of North America it appears that at present about 20 per cent of all cases of aseptic meningitis are due to poliomyelitis virus, 20 per cent to Coxsackie B, and a variable number of the remainder to ECHO and other viruses; however, it is obvious that these figures may vary considerably from year to year.

MANAGEMENT OF CASES OF ASEPTIC MENINGITIS

As viral aseptic meningitis is a relatively benign condition and responds to no specific drug therapy, as far as is known at present, the management is symptomatic. Isolation, bed rest, fluids, light diet and aspirin and codeine for the fever and malaise are usually all that are indicated. In some instances when vomiting is a prominent feature, intravenous fluids may be necessary to correct or prevent dehydration and maintain acid-base balance. Under ideal conditions the patient with aseptic meningitis should remain isolated until the diagnosis has been confirmed and such specific entities as non-glandular mumps, non-paralytic poliomyelitis and tuberculous meningitis have been reasonably well excluded by the history, physical examination, course of the illness, cerebrospinal fluid studies and virus cultures.

We have not found hot packs, physiotherapy or other adjuncts

necessary in these cases, since patients have all made satisfactory recovery on symptomatic therapy as outlined. Antibiotics are unnecessary if the diagnosis is definite; and when a number of cases have been seen, the syndrome is rarely confused with the conditions requiring specific antimicrobial therapy.

As the temperature subsides, usually in five to 10 days, and the patient commences feeling well, a gradual return to full activity is indicated. Isolation of the patient until clinical recovery is probably advisable. Follow-up lumbar punctures are unnecessary; however, in some of the patients in whom this procedure has been repeated we have been somewhat surprised to find a cerebrospinal fluid pleocytosis persisting for two to three weeks.

In the patients exhibiting the rash in conjunction with aseptic meningitis, this has gradually subsided, and the skin has returned to normal by the time clinical recovery has been attained in other respects, usually five to 10 days from the onset.

LABORATORY INVESTIGATION OF ASEPTIC MENINGITIS CASES

In order to compile significant statistical evidence on the aseptic meningitis problem, it would be advisable to obtain virus studies on each case of this syndrome diagnosed. Most large centres have virus laboratory facilities available which are at the disposal of private physicians as well as hospitals.

In Ontario, specimens from cases of aseptic meningitis should be forwarded to The Division of Laboratories, Ontario Department of Health, 360 Christie Street, Toronto, Attention: Virology Department. A short history, a sample of the patient's stool, cerebrospinal fluid, and acute and convalescent sera (i.e., 10 ml. of clotted blood taken during acute phase, and 10 to 14 days later) should be forwarded to the Laboratory. These specimens should be packed in ice, or, if possible, carbon dioxide snow and delivered as soon as possible. Animal inoculation, tissue cultures and virus neutralization tests are then performed and in many cases make a positive identification of the specific ætiological agent. Similar virus research centres throughout Canada and the United States, of course, are available for this service.*

In the Toronto area Dr. A. J. Rhodes, the Director of The School of Hygiene, University of Toronto, has organized a virus research unit. When notified by a practicing physician of an outbreak of a virus-like illness, a field worker from the group will be sent into the area to study the cases, collect specimens and give advice, if requested, on the management of the illness. By this method much valuable information on these viral diseases is being obtained. As this project is being supported mainly with funds from the National Health Grants programme of the Ontario and Federal Governments, this investigation is conducted at no expense to the patient or the physician in charge of the case.

* In the United States serum specimens, together with a concise clinical summary, may be sent to Virus and Rickettsia Section, Communicable Disease Center, Public Health Service, U.S. Department of Health, Education, and Welfare, P.O. Box 61, Montgomery 1, Alabama.

SUMMARY AND CONCLUSIONS

As one physician has aptly remarked, at this stage of the study of aseptic meningitis it would appear that there are many viruses looking for diseases, and many diseases looking for viruses!

It is questionable whether aseptic meningitis is a new disease syndrome. I believe the consensus is that it has been with us for many years, and has been passed over with the mistaken diagnosis of nonparalytic poliomyelitis, lymphocytic choriomeningitis or other conditions which, in reality, are probably much less common causes of the aseptic meningitis syndrome than recently isolated virus strains which appear to be more prevalent and widespread than formerly realized.

The multiplicity of viruses responsible for the clinical syndrome of aseptic meningitis which have already been isolated indicate that the search for the causative agents in this condition has only begun and that in epidemics or outbreaks of the future many more isolations of different specific viral strains undoubtedly will be made.

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SUPPURATIVE ADENOIDITIS

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I first met Emanuel Libman in 1920. He was then at the height of his fame, and his home was the mecca for the great and the near-great of the world: actors, opera stars, world-renowned physicians, educators, university presidents, together with awed and bewildered young men seeking aid for study abroad from one of the many funds he had at his sole disposal or from his own most generous pocket. He had been the personal physician to Lord Northcliffe, Sarah Bernhardt, Einstein and many other famed personalities in all parts of the world. Yet, whoever was with him, famous or unknown, however great the coterie, Libman monopolized the conversation. His showmanship demanded that he always occupy the centre of the stage; he was a great host, but a poor guest, and he loved being host. His talk bounced from politics to medicine to autobiography and to fascinating anecdotes interspersed with casually dropped clinical gems. He was at that time a living legend, a sharp-eyed, eccentric genius, world-famed for his uncanny and dramatic diagnostic ability. Dozens of diagnostic tricks and clinical signs were known as Libman's sign. Himself scrupulously honest intellectually, he hated deceit and intellectual dishonesty in anyone. He could overlook foibles and peccadillos and even ill-breeding in anyone gifted with scientific genius, and often supported and encouraged young men whom he personally disliked if he detected in them the makings of good investigators or first-class physicians.

My friendship with him lasted until his death, and from him I learned many things. What I wish now to write about concerns something he taught me in the course of a casual conversation in 1942. He frequently spoke of his interest in pædiatrics and liked to tell me on several occasions that he had, many years before, been offered the professorship of pædiatrics at Johns Hopkins. He refused this, he said, because of his far wider interest in general medicine and pathology.

It was on one of my visits with him that he offered to teach me

some pædiatrics. He had just published a short paper with the indeterminate title of "Notes on Clinical Observations and Methods, (II)," which appeared in the *Journal of the Mount Sinai Hospital* in the January-February issue of 1942. Neither the title nor the *Journal* would have attracted many pædiatric readers. The paper itself is a mixture of disconnected paragraphs dealing with some unusual clinical signs in tuberculosis, Hodgkin's disease, tracheal tug, and so on. The second paragraph, however, deals with suppurative adenoiditis. This is what Libman wanted to teach me. This was apparently his second case, because in a previous, equally disconnected paper with the same title, published in the same journal in the November-December issue of 1938, he had described a similar case. Both concerned children with prolonged and unexplained fevers lasting five or six weeks in which he searched carefully for a primary focus for a bacteræmia. "Finding none," he says, "in a careful examination of the body, I thought of an infected adenoid." He palpated the nasopharynx, found a large adenoid mass, and squeezed it with the examining finger. The fever disappeared on the following day, and subsequent recovery was rapid. The foregoing was his description of the second case; the first was essentially the same.

In his characteristic clipped, staccato speech he said to me: "If you will bear this in mind, you will many times find the cause of obscure prolonged fevers in children, and the very finding of the cause will cure them in less than 24 hours." Libman had a sure and uncanny instinct in diagnosis. His alert mind jumped directly into the very heart of a problem much as a mathematical genius solves an equation directly, apparently omitting those tedious, intermediate steps which lesser minds must laboriously tread.

I stored this information for future reference and use. There was no other literature on this subject and no references to Libman's dramatic method of cure; there were only the two obscure references which I should never have seen had he not spoken of them.

On my return to Montreal, by a fortuitous coincidence, not too rare in medical practice, I was that very morning asked by one of my pædiatric colleagues to see a child who had been admitted to hospital because of a fever which had lasted for some six weeks. A careful examination did not reveal any obvious cause for the illness; there was only the fever and nothing more. There were not even the slightly enlarged sentinel lymph nodes of which Libman had spoken. I decided to test his idea, and made a digital palpation of the nasopharynx. The space was almost completely occupied by a large boggy mass, and I pressed the examining finger into the folds. There was a little blood which must have obscured whatever pus I might have evacuated. That afternoon the child's temperature was normal; it remained so, and the child was discharged well.

This was in 1942. From that time on I have seen, and continue to see, a large number of similar cases each year. Libman had made the statement that any pus evacuated was masked by blood. I have found that when these children are seen in the office or hospital, it is not a matter of any great difficulty to determine whether pus is present. Before making the examination, I prepare a microscope slide with a few drops of dilute acetic acid or white blood cell count diluting fluid. I use a fingercot for the examination, then smear the evacuated material onto the slide, and the pus is clearly visible. In the few cases in which the diagnosis was wrong the smear showed a few lymphoid cells and some epithelium, but in the true instances the smear shows huge clumps of pure pus.

The technique is simple. The finger is passed into the nasopharynx and is pressed into each of the adenoid folds and withdrawn. If the smear is positive, the child is continued on antibiotics for two or three days. The temperature usually falls to normal within a few hours of the examination, rarely more than 24 hours later.

Most of these cases have a repetitious sameness in their histories, usually of a fever that has lasted six weeks or more, with elevated white blood cell and polymorphonuclear counts and of unrewarded search. It is not at all surprising that almost never have they been seen by an otolaryngologist, because nothing in the complaints or physical examination would suggest trouble in this area; occasionally there are enlarged nodes under the sternocleidomastoid, but rarely nasal discharge or any other phenomena which would suggest an otolaryngological consultation.

Since the first time that Libman called my attention to this condition and my fortuitous diagnosis a day or two later, I have seen an unending succession of this disease. It is by no means a rare condition, and each winter brings a continuous stream of these problems to my notice. The original throat infection is all but forgotten, and the child is seen only for the prolonged and unexplained fever. Direct questioning will bring out the story of a two- or three-day illness a month or so previously, a few days' freedom from fever and a resumption of a daily rise to 102° F. or higher. Frequently, but not always, the cervical gland under the sternocleidomastoids may be felt to be somewhat enlarged. The tonsils usually give no hint to the nature of the disease. The fever is evidently due to retained pus in the adenoid folds, sealed off and unable to drain. By pressing the examining finger into the folds, the pus is liberated, and the temperature falls. In most such instances it is perhaps wise to advise removal of the adenoids soon after the subsidence of the acute infection.

Most children have had no symptoms other than the malaise and the continued fever; in a significant number, however, occipital headache has been an outstanding complaint.

It might be well here to record the history of a few of these cases.

CASE I. A boy of 9 years was referred to me with the story that one year previously he had injured his head by diving into an empty swimming pool. Now, one year later, he began to complain of occipital headaches and afternoon fevers of one month's duration. Residual tonsillar inflammation and enlarged cervical glands made me enquire into the history of recent throat infections. The mother remembered that 5 or 6 weeks previously he had had a sore throat which responded to penicillin. A few days later the headaches began, and the fever returned. On palpation of the nasopharynx the adenoid mass filled the entire space. I pressed my finger into each of the folds and evacuated a good quantity of pus. The fever and headaches disappeared in less than 24 hours.

CASE II. A girl aged 12 who had an afternoon fever of 102° and 103° F. for more than a month had spent a week in hospital where she was intensively investigated. Beyond a blood picture consistent with a pyogenic infection, no focus was found. She was sent home and given a succession of antibiotics without any effect on the fever. The examination revealed nothing, not even enlarged lymph nodes. On examining the nasopharynx and pressing into the adenoid folds, I evacuated a sizeable quantity of pus with the almost joyful statement of the patient that she felt better already. It was late afternoon when I saw her; by evening the temperature fell to normal and remained so.

CASE III. A boy aged 8 years was brought with the complaint of anorexia, headache and weight loss of several weeks' duration. There was no complaint of fever, though it was elevated at the time of the visit. The tell-tale glands were enlarged, and palpation of the nasopharynx yielded a fair quantity of pus.

These are three typical experiences similar to what I encounter twice or three times a week during the winter months. The condition is doubtless far more common than is appreciated. Diagnosis depends on knowing that such a sealing off of pus is possible and making the necessary and simple examination. My own diagnostic resources would never have led me to think of such a possibility. My own clinical teachers had taught me that under similar conditions in an adult male one was to think of and examine for a prostatic abscess, but a pædiatric career is hardly the field in which to encounter such a condition. Had it not been for my conversation with Libman and his giving me a reprint of an obscure article, I should probably never yet have been aware of adenoid suppuration. Kudos and ridicule have followed this diagnosis. The only pædiatricians I have encountered who know of this condition and have successfully diagnosed and treated it seem to be those to whom I have called attention to Libman's articles. It is rather time that it be given a wider publicity and that Libman, man of amazing genius and equally amazing eccentricities, be given full credit for an important pædiatric observation.

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PNEUMOCYSTIS PNEUMONIA

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Pneumocystis pneumonia, or interstitial plasma cellular pneumonia due to *Pneumocystis carinii*, has recently been reviewed both in *Pediatric Clinics of North America*[1] and in *Pediatrics*.[13] The reason for a third review is to draw attention to an increase in the number of cases encountered recently in Canada.

The pathological features of this disease in infants were first fully described in 1938.[2] During the next two decades an increasing number of cases were reported, initially in Germany and Switzerland, but spreading gradually peripherally. In Switzerland Freudenberg and Tobler[12] encountered 707 cases between 1941 and 1949, in Germany Bachmann[4] was able to collect 120 cases seen between 1948 and 1954 and Harnack[18] 191 cases between 1950 and 1953, Reisetbauer[26] encountered 32 cases in Vienna in 1952 and 1953, while in Ljubljana a special isolation ward has recently been set aside for infants with this disease.[13] Ahvenainen[1] states that in Finland there have been more than 200 cases. Other reports have come from Czechoslovakia,[28] Hungary,[9] Italy[7] and Scandinavia.[29] In 1955 a case was reported from England[3] and another from the United States.[23] In the following year three cases were reported from Canada;[14] three have recently been seen in Australia.[27]

The first three cases from Canada were reported by Gagne and Hould[14] and were seen in Quebec; they occurred in 1953 and 1954. Donohue[11] next reported two cases of interstitial plasma cellular pneumonia subsequently identified as being due to *Pneumocystis carinii*; the first patient acquired the disease in the southern part of Saskatchewan in 1952 and died after an unusually long illness at the age of 17 months; the second was born in Ontario, ran a more typical course and died in 1954. Gerrard and Moore[15] next reported two cases in

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siblings from central Saskatchewan. The older child died in 1947 and the younger in 1956; both ran a typical course, though neither was premature. In the following year an additional case was recognized in Winnipeg.* Meanwhile, in 1955, Berdnikoff** had encountered two typical cases in Montreal, the first a boy who died at the age of two months and the second a girl who died at the age of three months. Berdnikoff subsequently reviewed the autopsy material at Ste-Justine's Hospital and has identified seven further cases, two girls and five boys all dying between the ages of two and four months; two were seen in

TABLE 12. *Cases of Pneumocystis Pneumonia Identified in Canada*

YEAR	NUMBER OF CASES	ORIGIN	REPORTED BY
1930	2	Montreal	Berdnikoff**
1935	1	Montreal	Berdnikoff
1936	1	Montreal	Berdnikoff
1941	1	Montreal	Berdnikoff
1947	2	Montreal	Berdnikoff
1947	1	Montreal	MacMillan[24]
1947	1	Saskatchewan	Gerrard and Moore[15]
1952	1	Saskatchewan	Donohue[11]
1953	2	Quebec	Gagne and Hould[14]
1954	1	Ontario	Donohue
1954	1	Quebec	Gagne and Hould
1955	2	Montreal	Berdnikoff
1956	1	Saskatchewan	Gerrard and Moore
1957	1	Winnipeg	Hoogstraten and McLandress*
Total	18		

* J. Hoogstraten and M. MacLandress: Personal communication.
** G. Berdnikoff: Personal communication.

1930, one in 1935, one in 1936, one in 1941 and two in 1947. To date 18 cases have been identified in Canada. (See Table 12.)

The first two cases occurred 27 years ago; the disease is therefore not a new arrival in Canada.* The cases so far reported have all been sporadic, and there have been no outbreaks as yet on the European scale.

CLINICAL FEATURES

The disease usually has its onset between the sixth and sixteenth weeks of life, though infants of six months and older may be affected; it is extremely rare in adults, though it has been reported in these.[24] Some 40 per cent of infants affected have been born prematurely.[12] It is contagious, and epidemics of the disease have been reported.[4] The incubation period is about 40 days.[4] The onset is insidious, and the initial symptoms—feeding difficulties and failure to thrive—are by no means specific; to these are added tachypnœa—the respiration rate

* G. Berdnikoff: Personal communication.

gradually rises to 80 to 120 per minute—and a dry, unproductive but persistent cough; cyanosis then becomes evident, and though the infant appears alert, he has an anxious, distressed facies. There is usually little if any fever. The alæ nasi are active, and there is obvious suprasternal, intercostal and subcostal recession on inspiration, but in spite of the infant's obvious respiratory embarrassment abnormal clinical findings in the chest are often remarkably absent. There may be a little or no impairment of resonance; on auscultation, air can be heard entering both lung fields freely, and the breath sounds are vesicular; there may be a striking absence of adventitious sounds, though scattered râles are heard from time to time. The clinical picture simulates closely that seen in infants with the so-called hyaline membrane. The cyanosis is relieved by oxygen, but the observer has only to raise the tent flap for a moment when examining the child for the cyanosis to return. The disease may run a rapid course, and the infant may die within a few days of the onset; more commonly he suffers for three to four weeks before succumbing, and occasionally the disease may last for many months as in Donohue's[11] first case. Death is not inevitable, but occurs in about 20 per cent of cases.[12] Those who survive make a slow but gradual recovery. The complication most commonly encountered is an interstitial emphysema.[13]

ROENTGENOLOGICAL AND LABORATORY FINDINGS

Roentgenological examination reveals a characteristic infiltrating consolidation which spreads peripherally from the hilum and is not lobar in distribution (Fig. 4); there is no pleural reaction, nor any hilar adenopathy. The white blood cell count is usually elevated, being 20,000 to 40,000 per cubic millimeter with 70 per cent neutrophils, many being non-segmented; an eosinophilia of 10 to 15 per cent is not unusual. These findings in conjunction with the clinical picture are sufficient to make a diagnosis of pneumocystis pneumonia probable. Confirmation is not always possible unless the infant dies. Skin tests, using lung extracts, have not been helpful, but there is evidence that a complement fixation test may be. The latter has been developed by Barta[5] and his colleagues, who used an alcohol-soluble antigen prepared from acetone-extracted dried lungs of fatal cases; in their experience the sera from 30 of 41 patients who recovered from pneumocystis pneumonia and the sera from 25 who died gave positive results.

In suspected cases, particularly if the infant is a boy, the serum gamma globulin should be estimated, since there have been three cases reported[6, 15, 19] (and others suspected) in which the gamma globulin levels were extremely low. Another abnormality seen on occasion is a high serum calcium.[1]

Fig. 4. Radiological appearances in pneumocystis pneumonia, illustrating the wide spread of the consolidation.

The disease has such a characteristic picture that, once seen, it will readily be recognized if encountered a second time, but when it is seen for the first time, the discrepancy between the cyanosis and the lack of clinical findings in the chest often makes the observer suspect that the child has some other disorder, e.g., congenital heart disease.

PATHOLOGICAL ANATOMY

At necropsy the lungs are found to be voluminous and do not collapse when the chest is opened. They are grey or greyish-pink, and firm, and sink in water. Section shows the affected areas, which may be discrete or involve the whole of the lung, to be firm, dry and greyish and raised a little above the cut surface. Areas of compensatory or mediastinal emphysema may be present. The bronchi contain only a little mucus. Hilar lymphadenopathy may be absent or slight.

Microscopy reveals the alveolar walls to be thickened with a great increase in reticulum fibres, and a widespread interstitial infiltration composed of lymphocytes and plasma cells. The alveoli are lined in many instances by large cuboidal epithelial cells, which often desquamate into the alveolar lumina and in the healing stages of the disease become fat-laden. These cells are also stated to phagocytose the para-

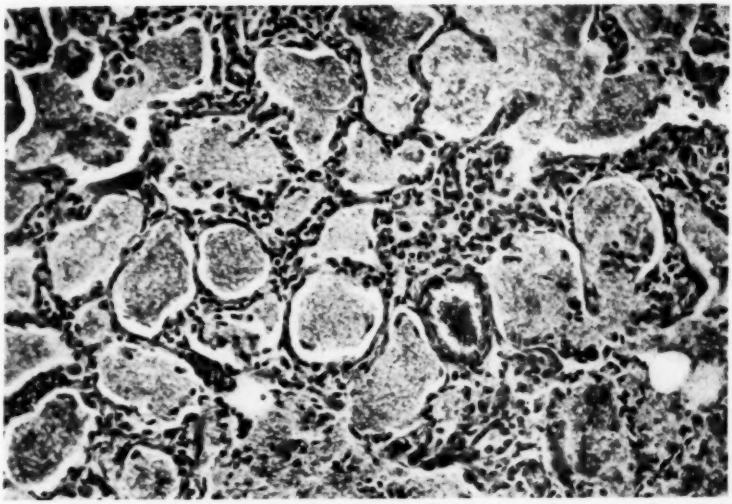

Fig. 5. Widespread intra-alveolar foamy material containing *Pneumocystis carinii*. H.E. magnification × 166, enlargement × 2.

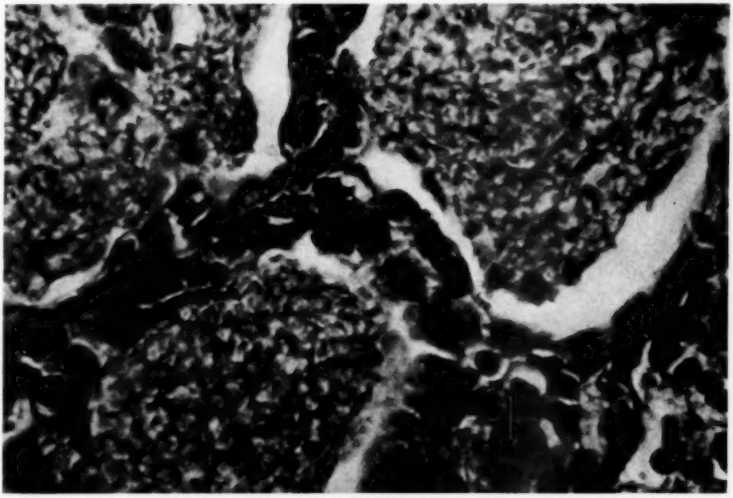

Fig. 6. Section of lung. Note cuboidal epithelium and numerous small bodies of *Pneumocystis carinii* in the alveolar exudate. H.E. magnification × 1000, enlargement × 2.

sites. In addition to desquamated alveolar epithelium, the alveoli contain, and are often packed with, a foamy material resembling a fine honeycomb, with vacuoles ranging from 4 to 10 microns in diameter. In this material can be discerned small compact masses 1 or 2 microns in diameter which take up chromatin stains. Vacuoles of parasites are also occasionally seen in alveolar septa. The foamy material is eosinophilic and stains with para-aminosalicylic acid. The compact granules are best stained with Gram-Weigert, toluidin blue or silver impregnation, according to the method of Lelong and Le-Tan-Vinh.[22] In impression or smear preparations from fresh-cut lung surfaces made at autopsy Giemsa staining is effective. Hamperl[17] has recently described what he considers to be a healing stage of the disease.

ÆTIOLOGY

There are three aspects of this disease which are of particular interest: (1) the nature of the infecting organism, (2) its relation to cytomegalic inclusion disease and (3) its association with hypogammaglobulinæmia and agammaglobulinæmia.

As to the ætiology, *Pneumocystis carinii* was first described by Chagas,[8] who believed it to be a developmental stage of *Trypanosoma cruzii*. It was later demonstrated that Pneumocystis occurred apart from trypanosomiasis, and it was generally considered to be a protozoan. Vanek and Jirovec[28] first identified this organism in the alveolar exudate of cases of interstitial plasma cellular pneumonia, and most workers are now in agreement that it is this organism which causes pneumocystis pneumonia, although it has still to be fully proved that this is so. An alternative suggestion, namely, that it is a fungus, Blastomyces, species Saccharomyces, has been put forward by Csillag and Brandstein;[9] these workers produced pneumonia in mice and rabbits from injection with this organism obtained from children dying of pneumocystis pneumonia, but the pneumonia in these animals lacked the intra-alveolar exudate. These studies also lack confirmation, but Ladstätter[21] claims to have grown the organism in culture.

The relation between cytomegalic inclusion disease and pneumocystis pneumonia has been noted by many and is discussed by Hamperl[17] and Gadjusek,[13] and though cytomegalic inclusions should be sought in all cases of pneumocystis pneumonia, the association of the two diseases probably indicates only that the infant with pneumocystis pneumonia is more susceptible to cytomegalic inclusion disease than the normal infant; there is probably no direct relation between the two diseases.

Pneumocystis pneumonia, as already mentioned, is most common in

infants between the ages of six and sixteen weeks, at a time when the serum gamma globulin level is at its lowest,[25] and it is therefore not surprising that there have been three reports of male infants dying of this disease who had an associated hypogammaglobulinæmia or agammaglobulinæmia.[6, 15, 19] What is surprising, however, is that these three infants each had a brother who had also died of pneumocystis pneumonia, and as the congenital form of agammaglobulinæmia is confined to males, the three brothers may well have had agammaglobulinæmia also. If agammaglobulinæmia is a common predisposing factor, it is strange that more cases have not been encountered in the United States, where this disease has been the subject of much intensive study.[16, 20] In this context it is not without interest that in the case reported by Dauzier *et al.*[10] an older child, dying at the age of 21 months, was a boy who had had frequent infections, mainly respiratory, but had also had a pericarditis and an otitis media, and even though he had had an adenoidectomy, it is possible that his susceptibility to infections may have been due to a low serum gamma globulin. If such children are particularly susceptible to pneumocystis pneumonia, then the causative organism must be widespread, for the three reported cases were widely scattered, and it must be assumed that many other children acquire the infection, but that these survive. In this context it should be mentioned that *Pneumocystis carinii* has been isolated from many animals, but since contact with the infants most commonly affected, namely, prematures, cannot be common, one can hardly postulate a direct spread from animals in such cases. It is more probable that subclinical infection in adults is more common than is at present realized and that it is from such unsuspected carriers that the infant acquires his infection.

TREATMENT

Careful nursing and high concentrations of oxygen and humidity are indispensable; feeding has often to be by gavage, since the infant is too distressed or unable to suck. Antibiotics, blood, convalescent serum, gammaglobulin, corticotropin and cortisone have, unfortunately, not been found to influence the course of the disease, and the same may be said of antiprotozoal agents. Antifungal agents should be given a trial, in view of the work of Csillag and Brandstein.[9]

SUMMARY

Eighteen cases of pneumocystis pneumonia have so far been identified in Canada. Nine of these cases occurred within the last six years,

but the first patient died 27 years ago, and the disease therefore cannot be considered to be a new arrival to this country. No epidemics have yet been encountered; all the cases have been sporadic.

I am very grateful to Drs. G. Berdnikoff, W. L. Donohue, J. Hoogstraten and M. McLandress for giving me access to their cases, and to Dr. H. Emson for his advice.

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IDIOPATHIC PULMONARY HYPERTENSION IN INFANTS AND CHILDREN

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Until recently the syndrome of idiopathic pulmonary hypertension was considered a disease primarily of adults. Although isolated cases have been reported in children, it is only in recent years that there has been much emphasis on this condition in the pædiatric age group. The current widespread interest in pulmonary hypertension in general, and as a complication of congenital heart disease, has been largely responsible for this. Information obtained by cardiac catheterization, when correlated with the clinical findings and histological changes, has increased our knowledge immeasurably. However, there is still much to be learned about pulmonary hypertension, and the subject is hampered by confusing terminology.

Many synonyms, such as "primary" or "essential" pulmonary hypertension, pulmonary arteriosclerosis with right-sided heart failure, Ayerza's syndrome, and others, have been used to describe this condition. In my opinion the term "idiopathic pulmonary hypertension" is preferable and has been adopted as the title of this paper. It describes the most noteworthy feature of the disease and acknowledges that the ætiology is still unknown.

The present report will describe the clinical characteristics of idiopathic pulmonary hypertension *in infants and children*. Our knowledge of the microscopic anatomy, diagnosis and management will be reviewed, and a simple classification will be outlined and discussed.

CLASSIFICATION

In the past the terms "primary" and "secondary" were commonly used in the classification of pulmonary hypertension. The designation of one

type as 'primary' is misleading because it has never been established that the pulmonary hypertension is due to obliterative vascular disease in the lungs. In fact, some evidence suggests that the opposite is true. For example, isolated right ventricular hypertrophy can occur without associated pulmonary vascular sclerosis,[15, 17] and pulmonary vascular sclerosis has been reported without right-sided heart hypertrophy.[6] To avoid this implication of a pathogenetic role which is not certain, a classification is suggested in which the term 'idiopathic' has replaced 'primary,' and the term 'secondary' pulmonary hypertension is reserved for that type which is truly secondary to a parenchymal lung disease.

Classification of Pulmonary Hypertension in Children

1. Hyperkinetic pulmonary hypertension
2. Idiopathic pulmonary hypertension
3. Secondary pulmonary hypertension

The pulmonary arterial systolic pressure is normally about one-fifth of the systemic pressure. Pulmonary artery pressures over 30 mm. of mercury in children are considered abnormally high. As in the systemic circuit, pressure depends upon two main factors: (*a*) the volume rate of flow and (*b*) resistance to the flow. Thus, with a given resistance, increased flow increases the pressure. Similarly, for the same rate of flow, increased resistance will cause a pressure rise. Moderate increase in both flow and resistance will also raise the pulmonary pressure.

Hyperkinetic Pulmonary Hypertension

This syndrome is due to an excessive volume flow of blood in the pulmonary circulation. It occurs physiologically in neonatal life and up to the age of three months. At this stage of development the proportion of blood flow in the pulmonary circuit is greater than that in adult life. The same mechanism occurs when a congenital cardiac anomaly permits an unusually high pulmonary blood flow. The commonest anomalies of this type are patent ductus arteriosus, ventricular or atrial septal defect and Eisenmenger's complex. Prolonged high flow in the lesser circulation leads to arteriolar medial hypertrophy, giving the pulmonary arterioles an appearance similar to that seen in the pulmonary arterioles in fœtal life and the peripheral arterioles in adult hypertension.[18]

Idiopathic Pulmonary Hypertension

This occurs when the resistance in the pulmonary vascular bed is increased. In this type the vascular narrowing is due to a combination of arteriolar medial hypertrophy, vasculitis and endarteritis. These lesions *appear* to be primary. They are not the result of abnormal

cardiac shunts. Although their cause is unknown, their histological appearance may resemble the changes seen in the systemic blood vessels in essential hypertension.

Secondary Pulmonary Hypertension

This occurs when pulmonary vascular obstruction is secondary to chronic lung disease. The most common pulmonary diseases which produce this syndrome in childhood are bronchiectasis, mucoviscidosis, asthma, atelectasis, congenital lung cysts, and multiple embolization.

HISTORICAL

The name of Ayerza[2] has long been associated with the triad of right-sided heart failure, cyanosis and obstructive pulmonary vascular disease. Actually, Ayerza did not describe the pathology of the pulmonary vessels. This was described later by three former students, Marty,[30] Arrillaga[1] and Escudero,[20] who coined the term 'Ayerza's disease.' They emphasized the pathological feature of pulmonary endarteritis, which they ascribed to syphilis. Brenner[6] in 1935 correlated, clinically and pathologically, pulmonary vascular sclerosis and right-sided heart hypertrophy in adults. He also listed the criteria for the clinical diagnosis of the syndrome, which are still valid. Since then, numerous authors[5, 7, 31] have amplified the pulmonary vascular changes and speculated upon their causal relationship to the cardiac changes.

Dresdale *et al.*,[16] in reporting three cases, included cardiac catheterization data correlated with pulmonary function studies. The hæmodynamics at rest and during exercise, and the effects of sympatholytic drugs were also studied. They reported greatly elevated pulmonary artery pressure, raised right ventricular and diastolic pressure, diminished cardiac output and normal arterial oxygen saturations. They calculated a ninefold increase in pulmonary resistance in some cases and felt that drugs such as Priscoline were effective in lowering the pulmonary artery pressure by decreasing the resistance to pulmonary blood flow. Chapman *et al.*,[10] in reporting 10 additional cases, including two children, found the pulmonary capillary pressure to be normal in the three patients on whom this measurement was possible. Berthrong[5] recently reported a pathological study of nine cases in infants and children. Most of these patients were catheterized and showed the characteristic findings of right ventricular and pulmonary arterial hypertension. The current *pædiatric* literature contains numerous other reports of idiopathic pulmonary hypertension substantiated, in most instances, by cardiac catheterization studies.[3, 4, 9, 24, 35, 37]

CLINICAL PICTURE

Characteristically, the symptoms of idiopathic pulmonary hypertension develop insidiously. They also vary considerably with the age of the child and the stage of the disease. In infants and children the early symptoms are breathlessness and fatigability. Later, symptoms of right-sided heart failure predominate.

Clinical Features in Infancy

The infant is normal at birth and usually appears healthy for the first few months. The first complaints are feeding difficulty and failure to thrive. The mother soon realizes that the infant is so easily fatigued that it is too tired to complete a feeding. It is this which contributes mainly to their appearance of debility and often initiates the desire

for medical advice. Soon thereafter, definite breathlessness is noted, and this is aggravated by any activity. Later, constant mild cyanosis is present. This is not as strikingly aggravated by crying as in patients with congenital cardiac anomaly. The breath sounds are normal unless there is an accompanying infection.

Polycythæmia sometimes accompanies the cyanosis. It is seldom associated with obvious clubbing and is not as marked as in cyanotic congenital heart disease.

Episodic pain, apparently due to pulmonary hypertension, has been noted frequently in infants.[3, 9, 24, 31] In one case observed personally an electrocardiogram was taken during an attack of pain, and no evidence of coronary insufficiency was demonstrated. Amyl nitrite also failed to modify the pain. The cause of this pain has been much debated, many accepting the view of Viar and Harrison[38] that it is the specific pain of pulmonary hypertension. In infants with pulmonary hypertension syncopal attacks occur rarely. Hæmoptyses are not reported.

On examination the infant usually appears debilitated. The heart is clinically enlarged, and the precordium may bulge anteriorly. The pulse rate is rapid and regular. The pulmonary second sound is accentuated. A pulmonary systolic murmur is usually heard, loudest in the second and third left interspaces close to the sternum.

Clinical Features in Childhood

In children, cyanosis is sometimes an early major presenting finding. This happened in six of Berthrong's patients.[5] The cyanosis is accompanied by breathlessness and extertional dyspnœa. Debility is also a common finding, and in these patients there is usually a past history of feeding difficulty and anorexia. Some patients, however, are moderately well nourished. Muscular weakness and extreme fatigue on exertion are so marked in some patients that they may even suggest the alternative diagnosis of myasthenia gravis or muscular dystrophy. Exertional syncope, a common symptom in adults with pulmonary hypertension, has not been reported as frequently in children. The episodic precordial pain described in infants (and adults) is not a feature of the clinical picture in children. The signs of congestive failure (venous distension, peripheral œdema and hepatomegaly) may appear early and overshadow other symptoms and signs in children.

On examination, right ventricular hypertrophy may be suggested by a precordial chest deformity. Palpation of a systolic sternal heave tends to confirm this. The pulmonary second sound is markedly accentuated, and a pulmonary systolic murmur is audible along the left

sternal border. Loud parasternal diastolic murmurs of the Graham Steell type have been reported in children with pulmonary hypertension, but their presence usually suggests some alternative diagnosis.

LABORATORY FINDINGS

X-ray of the Chest

There is a characteristic cardiac silhouette (Fig. 7). The postero-anterior view shows cardiac enlargement with prominent pulmonary

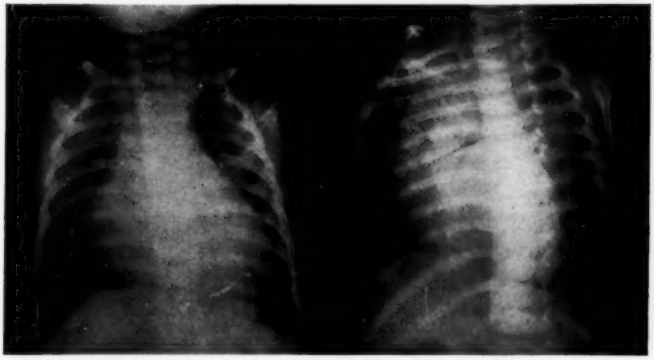

Fig. 7. Anteroposterior and left anterior oblique views of the heart in a case of idiopathic pulmonary hypertension. Note general enlargement of the heart and hypertrophy of the right ventricle.

hilar vascular markings. The peripheral lung fields are relatively avascular. In the lateral and oblique views, right ventricular hypertrophy is suggested by encroachment of the heart on the retrosternal space.

On fluoroscopy, although the pulmonary artery is dilated, the peripheral lung fields are relatively translucent.

The Electrocardiogram

The electrocardiogram shows right ventricular hypertrophy (see Fig. 8).

Blood

The red blood cell count, hæmoglobin and hæmatocrit may be above normal in cyanotic patients, but are not consistently raised. This is in contrast to the red blood cell count in patients with cyanosis due to a cardiac shunt. Since many children with pulmonary hypertension are

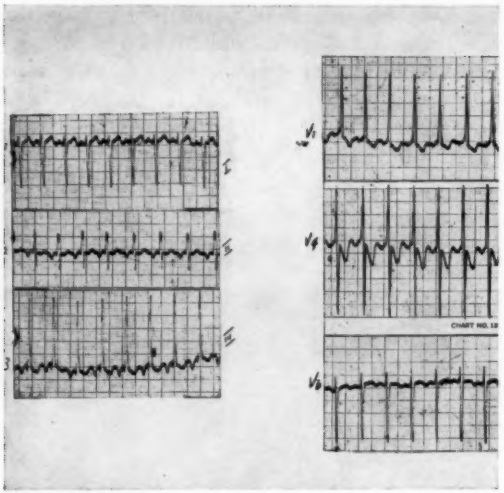

Fig. 8. Electrocardiogram of an infant with idiopathic pulmonary hypertension, showing the right ventricular hypertrophy pattern.

debilitated and therefore liable to nutritional anæmia, they may not show the expected polycythæmia. The degree of oxygen desaturation in these patients is not as high as that seen in congenital heart disease with large right-to-left shunts. Berthrong[5] could not explain the cyanosis in some of his patients with pulmonary hypertension by alteration of the rate of oxygen diffusion across the alveolar membrane. All the cyanotic patients in his series had slight anatomical patency of the foramen ovale sufficient to allow right-to-left shunt when the pressure is higher on the right (see Fig. 9). Mild cyanosis with slight oxygen desaturation is sometimes reported in these patients with pulmonary hypertension and no intracardiac shunt. An arterio-venous aneurysm in the lungs (pulmonary artery to bronchial) has been postulated to explain the cyanosis in these cases.

Cardiac Catheterization

Cardiac catheterization has been done in many children with pulmonary hypertension. This procedure, although attended by some risk in this age group, is of value in exact measurement of pressures in the pulmonary artery and right ventricle and may be necessary to exclude a congenital cardiac defect. Measurements of the oxygen saturation and of the cardiac output are also of value in diagnosis. The pulmonary artery and right ventricle pressures are *always* high and sometimes equal to or greater than that of the systemic circulation. The degree

of oxygen desaturation is rarely marked. Typical pressure and oxygen saturation measurements in the various heart chambers are illustrated in Figure 9. Dresdale *et al.*[16] measured the cardiac output and found it to be diminished. They also recorded normal arterial oxygen saturation in their patients. Measurement of pulmonary capillary (wedge) pressure may be of some value in excluding left-sided heart failure.

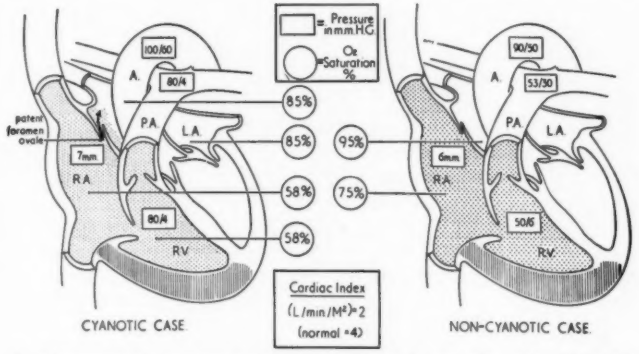

Fig. 9. Diagrammatic representation of the heart of patients with idiopathic pulmonary hypertension, showing the expected pressure and oxygen saturation values in a cyanotic and a non-cyanotic case.

However, left-sided heart catheterization should prove to be more useful in this respect.

Angiocardiography

Angiocardiography is seldom indicated, although it may reveal a right-to-left shunt through a patent foramen ovale.

Warning

Some patients with pulmonary hypertension do not tolerate these diagnostic procedures well. Sudden decreases in cardiac output which may occur with induction of anæsthesia or the introduction of a catheter may be rapidly fatal. Such accidents have been reported in association with such simple procedures as estimation of the circulation time.[14] These children should therefore be treated with special care during fright-making procedures and any activities which are liable to produce sudden pressure changes in the pulmonary circuit.

COURSE AND PROGNOSIS

The outlook varies considerably with the age of the child and the severity of the disease. Mild degrees of pulmonary hypertension in

young children may cause no symptoms at all. Those patients in whom the hypertension is sufficient to produce symptoms in infancy usually die before the age of two. In children the symptoms of pulmonary hypertension may remain stationary for several years until a severe pulmonary infection aggravates the condition. This frequently happens at puberty. Occasionally pregnancy may be the precipitating factor. Authors describing pulmonary hypertension in adults give a variable prognosis. Wood[40] mentions an average survival of two years after the onset of symptoms, and yet most series contain reports of patients observed over periods of 10 or more years. Reports of survival over longer periods (more than 10 years) have appeared.[4]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Although, when taken singly, the symptoms outlined above are not diagnostically specific, yet the above-mentioned combination of history, physical signs and laboratory findings should indicate the *possibility* of pulmonary hypertension. Unexplained right-sided heart failure in the absence of findings which confirm a congenital cardiac anomaly or primary lung disease should suggest this diagnosis.

The most obvious differential diagnosis is *congenital cardiac anomaly*.[31] In the past many patients with idiopathic pulmonary hypertension were erroneously placed in this category. *Careful consideration of the clinical, electrocardiographic and radiologic findings will usually reveal some inconsistency with one of the cardiac anomalies in which right-sided heart hypertrophy is a feature.* Or, conversely, some other identifying sign or symptom usually present in a particular congenital anomaly will be lacking. When such a dilemma occurs, the possibility of pulmonary hypertension should be considered and additional evidence for this diagnosis sought. To decide the issue, it may be necessary to refer the child for cardiac catheterization. If doubt still exists, thoracotomy and lung biopsy may be necessary.

Pure *pulmonary stenosis* may simulate idiopathic pulmonary hypertension. The loud pulmonary systolic murmur and the diminished pulmonary second sound combined with post-stenotic dilatation of the pulmonary artery should identify this condition. Catheterization findings of a high right ventricular pressure and low pulmonary artery pressure would confirm this diagnosis.

Two other causes of cardiac failure and hypertension may have to be eliminated: viz., *fibro-elastosis* and *glycogen storage disease* of the heart. In neither case is there radiologic or electrocardiographic evidence of isolated right ventricular hypertrophy. Extreme muscular hypotonia and characteristic muscle biopsy findings will also be seen in cardiac glycogen storage disease.

Pulmonary hypertension due to diseases of the lungs such as fibrocystic disease will have to be excluded. This can usually be done radiologically or on the grounds of history, but usually the symptoms of the primary lung disease overshadow those of the cardiac complication.

In summary, then, the diagnosis depends upon an awareness of this condition and the exclusion of alternative diagnoses.

PATHOLOGY AND PATHOGENESIS

The anatomical changes in the heart are simple and easily explained. The enlargement is due to extreme hypertrophy of the right ventricle

Fig. 10. Photograph of the heart of an infant with idiopathic pulmonary hypertension, showing the hypertrophy of the right ventricle and atrium.

(see Fig. 10), whose wall may be thickened to three to five times normal. The valves and endocardium are normal, and no anatomical anomaly of the septa or great vessels is seen. Sometimes the foramen ovale is functionally patent, so that a small right-to-left shunt may occur if the pressure in the right atrium is extremely high. This would account for the variation in degree and onset of cyanosis that is reported in these patients (Fig. 9). The pulmonary truncus and main pulmonary artery are dilated; and sometimes atheromatous plaques are seen in their walls. Microscopically, there is simple hypertrophy of otherwise normal fibres, and the coronary blood vessels are normal in size and architecture.

Gross anatomy of the lungs is non-specific. They may show patchy atelectasis and terminal pneumonic consolidation. Extensive thrombosis or embolization is not usually seen. Other viscera are normal.

The pulmonary histology is variable and complex. The distinctive changes occur mainly in the small arteries, arterioles and pre-capillary arterioles. They are generally of three types: *medial hypertrophy, fibrosing endarteritis,* and *necrotizing arteritis.*

The *arteriolar medial hypertrophy* (Figs. 10, 11) may be simple hypertrophy, or the lumen may be narrowed by loose, atypical muscle

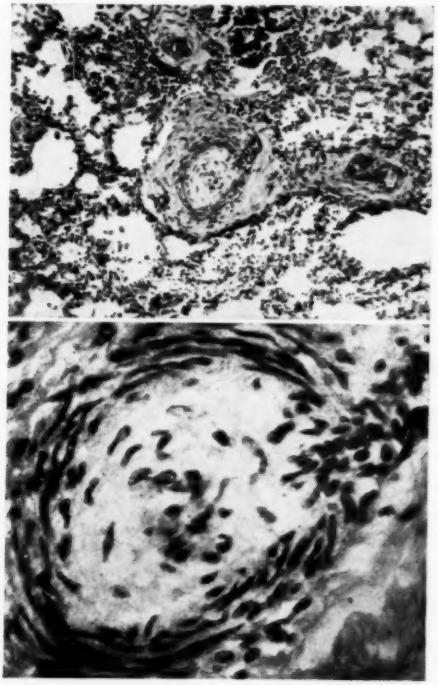

Fig. 11. *Upper,* Obliteration of lumen in a small muscular artery by loose, hypocellular material. The arteriole above this vessel shows muscular disarray in the subintimal zone.

Lower, Higher power view of the vessel pictured in Figure 10. The mucoid appearance of the inner media is very evident. A small tributary is arising in the upper right aspect. Contrast with Figure 13.

tissue with bulky, soft-appearing intercellular substance which suggests the structure of fœtal embryonic vessels. It has also been described by Civin and Edwards[12] and Edwards and Chamberlain[19] in the pulmonary vascular lesions associated with large left-to-right shunt. In fœtal life these vessels serve a protective function by diverting blood to the systemic circulation via the ductus, and their persistence in shunt cases may serve a similar purpose.[18]

Fibrosing endarteritis combined with *arteriolar medial hypertrophy* is found in the systemic vessels in "essential hypertension." Such changes have been reported in the pulmonary blood vessels in idiopathic pulmonary hypertension (Figs. 12, 13). Gilmor and Evans[21] have suggested that this is possibly part of a congenital defect of the media

Fig. 12.

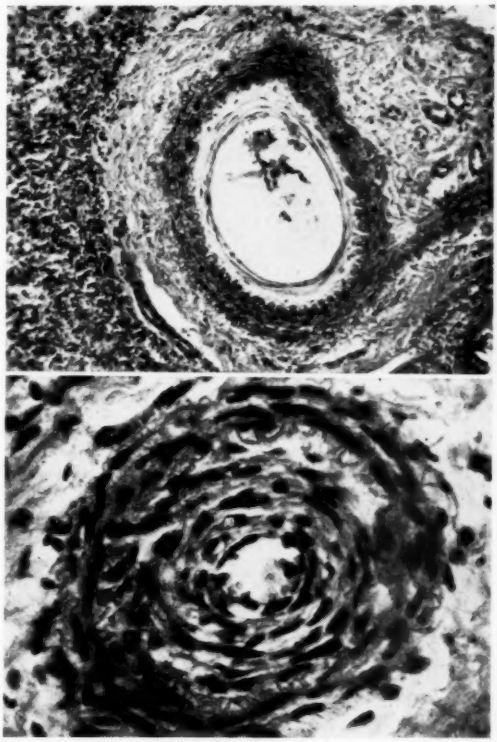

Fig. 13.

Fig. 12. A medium-sized muscular artery showing elastosis and endarteritis fibrosa.
Fig. 13. Vessel of arteriolar size showing concentric muscular hyperplasia associated with hypertension. Note the definite internal and external elastic laminæ, which are not normally present in vessels of this calibre.

which is compensated for by intimal proliferation. The possibility that the vascular lesions are part of a congenital vascular anomaly is supported by the occasional report of this disease in siblings[3, 25, 27] or in families.[32]

Necrotizing arteritis (Fig. 14) is commonly associated with other vascular changes in malignant hypertension, and some authors[27, 36]

consider that a similar process may occur in the lesser circulation. However, in some cases this lesion simulated that seen in periarteritis nodosa (Fig. 15).[29] Some authors have postulated an infective or allergic ætiology, but this has never been confirmed by discovery of a causative infection or allergen. Necrotizing arteritis may also be caused

Fig. 14.

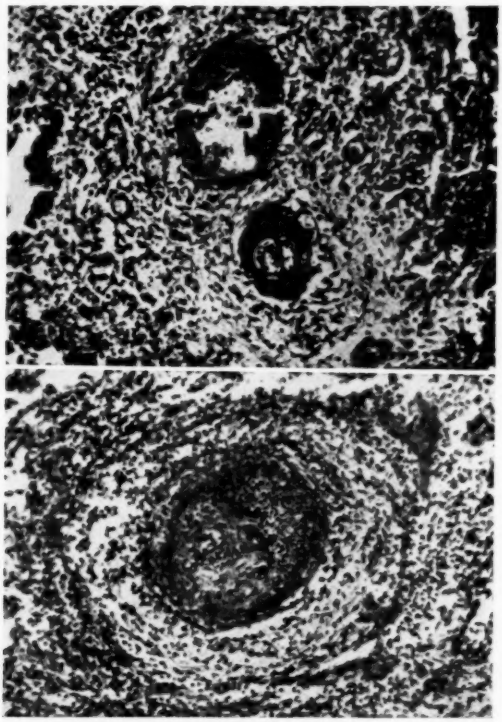

Fig. 15.

Fig. 14. Necrotizing arteritis involving a small muscular branch and an adjacent arteriole. There is fibroblastic proliferation of the adventitia and in the perivascular region.

Fig. 15. Acute inflammatory arteritis simulating periarteritis nodosa.

by a sudden increase in the pulmonary blood flow. This is confirmed by the observation of necrotizing arteritis and thrombosis in the mesenteric arteries due to excess volume flow of blood following a successful repair of aortic coarctation.[22] The experimental work of Muller and Damman[34] lends further support to the view that such lesions may be caused by increased blood flow in the lesser circulation.

Anoxia and embolization are the two other factors which are thought

to be important in the pathogenesis of this disease. Campbell[8] produced experimental pulmonary arteriosclerosis in cats by chronic hypoxia, and Cournand[13] has presented evidence which suggests that recurrent anoxia may produce pulmonary hypertension by changing vasomotor tone in the pulmonary vessels which later leads to arteriosclerosis. James and Rowe[26] have recently shown in acute experiments in infants that hypoxia will raise the pulmonary blood pressure.

Thromboses in all stages of repair have been seen in cases of obliterative pulmonary vascular disease. It is also known[23, 33] that organized multiple pulmonary thrombi may simulate arteriosclerosis. Muirhead and Montgomery[33] have also produced pulmonary hypertension experimentally by embolization with microscopic blood clots. Experimental studies have shown that necrotizing arteritis may also be produced in this way.[34] Minute pulmonary emboli and organized thrombi may also occur as part of the process of an intense pulmonary arteritis.[23, 29, 33, 39] Knisely *et al.*[28] consider that sludging of the blood may predispose to thrombosis. Berthrong[5] suggests that polycythæmia and thrombosis in the umbilical vein or the vena cava should be investigated as possible sources of pulmonary emboli. However, no solid evidence exists that such a process actually occurs in pædiatric patients.

From the foregoing comments it will be apparent that the identification of cause and effect between pulmonary hypertension and the associated vascular obliterative changes has not been established. This relationship has been interminably discussed, but never settled. The problem may not be resolved until the pathological physiology of the control of vasomotor tone of the pulmonary arterioles is more completely understood. It seems possible that a functional rise in the intraluminar pressure due to raised vascular tone or increased blood flow or viscosity may be the mechanism involved.

MANAGEMENT

Unhappily, the improvement in the diagnostic possibilities in this disease has not been paralleled by an equal advance in our knowledge of treatment. That the pathological changes might be arrested or reversed is suggested by the current possibility of success in the drug treatment of essential hypertension. However, in the past, therapy did not alter the ultimate prognosis, and no specific treatment of proved value has been discovered. Oxygen will give symptomatic relief from dyspnœa and cyanosis. Regular inhalation of oxygen for 15 minutes four times daily is advised as symptomatic treatment. As a low cardiac output is often present,[16, 18] digitalis and other ancillary measures should be used in standard dosage when symptoms and signs of congestive failure are present. A low salt diet is indicated. Mercurial di-

uretics and Diamox are advised for control of œdema. Rest and mild sedation are important.

Cortisone and Priscoline are two agents which on theoretical grounds might prove helpful. If the necrotizing arteritis was a manifestation of hypersensitivity, it might be controlled by steroid therapy. Cortisone has been used without success in one case by Berthrong,[5] but the newer cortisone derivatives deserve wider clinical trial. Priscoline, an adrenolytic and sympatholytic agent, temporarily reduces pulmonary artery pressure and increases pulmonary blood flow (Chess and Yonkman[11]). This suggested a trial of surgical stripping of the sympathetic nerve supply to the lungs. The results in a few cases have been disappointing, as has the clinical trial of Priscoline.[14] The use of the newer hypotensive drugs in this disease has not been reported as yet.

SUMMARY

The clinical and pathological characteristics of idiopathic pulmonary hypertension in infants and children have been reviewed. Fatigability, progressive breathlessness, variable cyanosis, episodic chest pain, when combined with an enlarged heart, a left parasternal systolic murmur, a loud pulmonary second sound and x-ray and electrocardiographic evidence of right ventricular hypertrophy should suggest the possibility of pulmonary hypertension. If no additional evidence of a congenital cardiac anomaly or primary lung disease is discovered, the diagnosis of pulmonary hypertension should be strongly suspected. Direct measurement of the pulmonary blood pressure by cardiac catheterization may then be indicated. Appropriate treatment has been reviewed, but at present this is not curative, and the ultimate prognosis is poor.

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NEWER LABORATORY PROCEDURES

Their Application to the Investigation of Pædiatric Disorders

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As medicine advances from an art to a science, the practitioners of the art adopt the scientific method of measurement and experiment in both diagnosis and treatment. Each year the laboratory enhances the clinician's senses by making available to him new techniques for more accurate diagnosis of disease and for more accurate evaluation of therapy. It cannot come within the scope of this brief review to encompass all such advances. The place of the laboratory in certain areas only will be discussed. A review of common useful laboratory procedures in pædiatrics appeared in an earlier volume of this publication.[71]

BLOOD

The diagnosis of most hæmatological abnormalities lies in the history and physical examination of the patient supplemented by a "routine" examination of the peripheral blood. We shall only refer in passing to the standard peripheral blood examinations, which are in reality the most important laboratory tests, and go on to discuss those tests and diagnostic procedures which may be called upon when the diagnosis is not readily apparent or when additional evidence is required.

THE ANÆMIAS

Impaired Red Cell Production

Hypochromic microcytic anæmia is most often the result of iron deficiency because of inadequate iron intake, malabsorption or blood

loss. However, the morphological picture may be simulated by the anæmia associated with copper or pyridoxine deficiency, lead poisoning, and by some of the hæmoglobinopathies. Depletion of body iron stores, as demonstrated in the adult by the absence of stainable iron (hæmosiderin) in the bone marrow, a low serum iron, and an increased total iron-binding capacity, is subject to different interpretation in the child. Smith *et al.*[79] found little stainable iron in the bone marrow of normal children under five years of age and could not distinguish the normal from the iron-deficient children on this basis. Although Smith, Schulman and Morgenthau[77] report the mean serum iron in the first six months to be 132 micrograms per 100 ml., closely approximating that of the normal adult, Sturgeon's[82] mean value of 53 micrograms per 100 ml. is a level well below the normal range for the older age groups. The total iron-binding capacity of both studies[77, 82] is about 400 micrograms per 100 ml., well above the normal adult level of about 350 micrograms per 100 ml. The technique of estimating the percentage of normoblasts with stainable iron granules (sideroblasts) in the marrow as outlined by Kaplan, Zuelzer and Mouriquand[48] would seem to be a simple method of establishing the presence of iron deficit. In iron deficiency anæmia the percentage of sideroblasts is reduced to 0.5 to 15 per cent from the 20 to 90 per cent found in normal infants. This difficulty in assessing mild or moderate iron deficiency may have arisen because many of the currently accepted "normals" may have indeed been iron-deficient.[82]

The *anæmia of iron deficiency* is characterized by a low serum iron, a high total iron-binding capacity and a high serum copper.[14] The normal adult serum copper averages 105 micrograms per 100 ml.,[51] but in infancy it is considerably higher—up to 146 micrograms. Recently cases simulating iron deficiency anæmia of infancy have been described in which the serum copper is low.[83, 85] In this hypochromic microcytic anæmia characterized by hypocupræmia the serum copper has ranged from 24 to 68 micrograms per 100 ml. The serum iron is low, and there is a moderate reduction in the total iron-binding capacity. The serum protein concentration is reduced, the hypoproteinæmia being characterized by a uniform reduction in the concentration of albumin and all globulin components. The hypoproteinæmia is such that œdema is usually present.

The *anæmia of chronic infection* is the result of impaired erythropoiesis and shortened erythrocyte life span. The red cells are usually normocytic and normochromic. The serum iron is low, the total iron-binding capacity reduced, and the serum copper is elevated.[15] The *anæmia of chronic renal disease* is also due to impaired erythropoiesis and shortened red cell survival and may be exaggerated by fluid retention, hypervolæmia and hæmodilution. There is no consistent alteration

in serum iron or copper. It is always associated with non-protein nitrogen retention.

Hypochromic microcytic anæmia responsive to pyridoxine is probably due to either an absorptive defect or metabolic aberration in the utilization of this vitamin. Although the only documented case is in an adult,[36] the incidence of pyridoxine deficiency in infants suggests that additional cases may be found in this age group. In the absence of adequate pyridoxine levels the conversion of tryptophane to nicotinic acid is partly blocked at the point of conversion of 3-hydroxykynurenine to 3-hydroxyanthranilic acid which requires pyridoxal phosphate. The 3-hydroxykynurenine is shunted through another pathway to form xanthurenic acid, which is excreted in the urine. This is the basis of the tryptophane loading test,[87] in which tryptophane is given by mouth and the degree of xanthurenic acid excretion is an index of pyridoxine deficiency. The reticulocyte response and rise in hæmoglobin when pyridoxine is given parenterally are diagnostic. In congenital hypoplastic anæmia the metabolism of tryptophane is blocked at an earlier stage, and anthranilic acid is excreted in the urine.[3]

The *megaloblastic anæmias* of infancy and childhood are usually due to folic acid and ascorbic acid deficiency. The older child may have megaloblastic anæmia due to dietary deficiency, cœliac disease, intestinal strictures or fistulæ, ingestion of the anticonvulsants primidone, sodium phenytoin or barbiturates,[6, 29, 39] or true pernicious anæmia.[62, 81] The serum vitamin B_{12} concentration is always low in pernicious anæmia and frequently reduced in nutritional megaloblastic anæmia, idiopathic steatorrhœa and intestinal anatomical defects, and normal in those anæmias due to anticonvulsant therapy.[6, 56] Oral vitamin B_{12} labelled with radio-active cobalt (Co^{60}) is a convenient method for assessing vitamin B_{12} absorption from the gastrointestinal tract. The Co^{60} excreted in the urine after a "flushing dose" of non-radio-active intramuscular vitamin B_{12} is an index of its absorption.[67] When vitamin B_{12} absorption is defective, less than 5 per cent of the oral dose is carried out in the urine in 24 hours. In true pernicious anæmia this defect can be corrected by repeating the test and supplementing the oral radio-active cobalt B_{12} with an exogenous source of oral intrinsic factor. When bowel pathology exists, vitamin B_{12} absorption is improved little, if any, by the addition of intrinsic factor.

Anæmia Due to Blood Loss

The development of anæmia due to bleeding may occur either *ante partum* or *post partum*. When bleeding occurs *in utero*, the child may be born showing evidence of blood loss. This bleeding takes place from the fœtal surface of the placenta, and blood may pass into the maternal

circulation or externally into the vagina. Chown[16] was the first to present evidence for fœtal bleeding into the maternal circulation. This was documented by the transient increase of fœtal hæmoglobin (hæmoglobin F) in the maternal circulation along with cells serologically identified as those of the infant. Subsequently several reports of fœtal cells entering the maternal circulation have been recorded. A further technique has been used which lends indirect evidence to support the passage of fœtal antigen across the placenta. Dunsford[26] has shown transient disappearance of anti-A agglutinins followed by a rapidly rising titre in group O mothers delivered of group A infants when bleeding into the mother presumably took place.

The quantitation of hæmoglobin F is also most useful in determining the presence of fœtal blood in blood passed *per vaginam* by the mother. By the method of Singer *et al.*[76] the hæmoglobin F content of normal adults is less than 2 per cent. The values in newborn infants range from 50 to 90 per cent. In the absence of the rarer hæmoglobin diseases such as thalassæmia or sickle cell anæmia the presence of more than 2 per cent hæmoglobin F is indicative of the presence of fœtal blood—the amount of admixture of fœtal and maternal blood can be roughly approximated by estimating the amount of fœtal hæmoglobin present.

The presence of dark blood in the stool of the newborn within the first 24 hours of birth raises the problem as to whether the child is bleeding or whether this merely represents maternal blood swallowed during passage through the birth canal. The answer can readily be obtained by making a watery extract of the stool and qualitatively determining the presence of hæmoglobin F in the extracted hæme pigment by its rate of alkaline denaturation.[4]

Anæmia of Blood Destruction

The determination of the erythrocyte life span is a valuable technique in the study of hæmolytic disease. The methods of differential agglutination or hæmolysis are accurate, but technically difficult. The use of Cr^{51} labelling of red cells provides a rapid, simple method for determining red cell survival in the adult. The survival time of the red cells of newborns as measured by differential agglutination would seem to be the same as or, at most, slightly less than the adult—100 to 120 days.[57] The radio-active chromium studies on newborn erythrocytes, however, indicate a relatively short red cell life span.[41] This discrepancy would seem to indicate a more rapid elution of chromium from the newborn erythrocytes than from the adult cell with an apparent shortening of red cell survival. It has been demonstrated *in vitro* that Cr^{51} can be eluted from fœtal hæmoglobin three times as rapidly as from adult hæmoglobin.[84] In view of these findings it

would seem that, aside from radiation hazards, Cr^{51} may not be a satisfactory agent for the determination of erythrocyte survival in the newborn.

The hæmolytic anæmias due to extra-corpuscular factors often exhibit normal red cell morphology; occasionally spherocytosis or Heinz bodies may be present. The hæmolytic diseases due to intrinsic red cell defects frequently show morphological abnormalities such as sickle cells, microspherocytosis, elliptocytosis, target cells or hypochromic microcytic forms. By the use of antihuman globulin serum (Coombs' test)[18] the acquired hæmolytic anæmias can often be identified by the demonstration of antibody on the cells or in the serum. Those anæmias due to intrinsic cellular structural or hæmoglobin defect almost always have a negative antiglobulin test. In those cases in which spherocytes are present the osmotic fragility is supportive evidence of congenital spherocytosis. The 24-hour incubation of defibrinated blood will induce a decided increase in osmotic fragility in the congenital spherocytic cells.[95] This is frequently useful when the spherocytosis is mild and when little increase in osmotic fragility is apparent on examination of unincubated cells. The hæmoglobin diseases can be diagnosed and categorized only by the identification of the abnormal pigment by electrophoresis, solubility, and alkali resistance studies.[44]

LEUCOPENIA AND THROMBOCYTOPENIA

The finding of a diminution in number of cells in the peripheral blood associated with marrow hyperactivity in this cell series is usually indicative of peripheral destruction of that cell. In the case of the leucocytes and platelets this is frequently due to an immune mechanism which may be set in motion by chemical agents or by auto-immunization. The altered cell or cell-drug complex is antigenic and produces an immune response with formation of antibody capable of agglutinating the cells and causing their removal from the peripheral blood. These antibodies may be demonstrated *in vivo* by transfusion—the transfused blood from the affected patient producing leucopenia or thrombocytopenia in the recipient. Demonstration *in vitro* is by agglutination of the leucocytes or thrombocytes by the antibody-containing serum.

The leucopenia complicating drug ingestion such as amidopyrine and sulfapyridine is often on an immune basis.[55] The leucopenia-producing factor in the serum of the patient will cause a sharp drop in the leucocytes of a normal recipient who has been given a preparatory dose of the drug. The leucocyte agglutinin may be demonstrated *in vitro* by incubating the test serum with a leucocyte suspension either in the test tube or as a slide agglutination procedure.[54] Leucopenia due

to immune anti-leucocytic mechanisms has been observed in virus pneumonia, infectious mononucleosis, involvement of the spleen in tuberculosis, sarcoidosis and brucellosis, as well as in various lymphomas.[53]

Platelet agglutinins have been demonstrated *in vitro* in idiopathic thrombocytopenic purpura and in neonatal thrombocytopenia.[34, 68] Neonatal thrombocytopenia includes those cases in infants whose mothers are thrombocytopenic and in which the platelet antibody presumably crosses the placenta and produces thrombocytopenia in the infant, as well as those in which the mother is not thrombocytopenic. In the latter the mechanism is presumably analogous to erythroblastosis with maternal iso-immunization to fœtal platelets.[34] Platelet agglutinins may be demonstrated *in vitro*, using the test serum against a number of platelet suspensions. Antihuman globulin tests (Coombs) on the platelets have been positive in some cases.[27] Similarly, thrombocytopenia following drug ingestion (Sedormid,[2] quinine[35] or quinidine[7]) can be demonstrated to be due to platelet agglutinins produced as a response to platelet-drug antigenic stimulus. This can be demonstrated *in vitro* by platelet agglutination tests as well as in some cases by the fixation of complement by the platelet-antiplatelet complex.[2]

A word of caution should be added in the interpretation of the leucocyte and platelet agglutination tests. Our knowledge concerning platelet and leucocyte groups is far from complete. It is difficult to interpret agglutination tests in the absence of this important information. The techniques are difficult, since leucocytes and platelets tend to adhere to glassware and to each other, so that falsely positive results are rather frequent.

COAGULATION

During the past two years numerous excellent reviews have been published outlining the mechanism of clotting and describing the tests used to identify the defects in the various bleeding diseases. Such a review appeared recently in this journal.[69] We shall only outline in table form the well recognized defects in the clotting mechanism and the commonest tests used in their identification (Table 13).

GASTROINTESTINAL TRACT

MALABSORPTION SYNDROME

This broad heading includes a variety of diseases such as sprue, giardiasis, fibrocystic disease of the pancreas, intestinal atresia and anastomosis. Certain recently developed techniques have made diagnosis in this area easier and more widely applicable.

TABLE 13. *A Number of Well-Documented Bleeding Diseases and the Commoner Tests Used in Their Identification*

	CAPILLARY FRAGILITY	BLEEDING TIME	CLOTTING TIME	CLOT RETRACTION	ONE-STAGE PROTHROMBIN TIME: THROMBOPLASTIN TISSUE	ONE-STAGE PROTHROMBIN TIME: RUSSELL VIPER VENOM	PROTHROMBIN CONSUMPTION	ASSAY FOR: FACTOR V	ASSAY FOR: FACTOR VII	ASSAY FOR: PROTHROMBIN	DEFECT IN: THROMBOPLASTIN GENERATION TEST: $Ba\ SO_4$	DEFECT IN: THROMBOPLASTIN GENERATION TEST: PLASMA	DEFECT IN: THROMBOPLASTIN GENERATION TEST: SERUM	FIBRINOGEN	FIBRINOLYSIN	ANTITHROMBIN TITRE
Normal newborn	−	−	−	−	+	+	±	±	+	+	−	+	−	−	−
Scurvy	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Purpura simplex	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Von Willebrand-Jürgens	+	+	−	−	−	−	±	−	−	−	±	±	−	−	−
Thrombocytopenia	+	+	−	+	−	−	+	−	−	−	−	±	−	−	−
Thrombocytoasthenia	+	+	−	±	−	−	±	−	−	−	−	−	−	−	−
Deficiencies of congenital and acquired: factor V	−	+−	+−	−	+	−	+−	+	−	−	−	−	−	−	−
Deficiencies of congenital and acquired: factor VII	−	−	+−	−	+	−	+−	−	+	−	−	−	−	−	−
Deficiencies of congenital and acquired: prothrombin	−	−	+−	−	+	+	+−	−	−	+	−	−	−	−	−
Circulating anticoagulant	−	−	±	−	±	±	±	−	−	−	−	−	−	−	±
Deficiencies of defects in thromboplastin formation: AHG	−	−	+−	−	−	−	+	−	−	−	+	−	−	−	−
Deficiencies of defects in thromboplastin formation: Xmas	−	−	+−	−	−	−	+	−	−	−	−	+	−	−	−
Deficiencies of defects in thromboplastin formation: PTA	−	−	+−	−	−	−	+−	−	−	−	+	+	−	−	−
Deficiencies of defects in thromboplastin formation: Hageman	−	−	+	−	−	−	+	−	−	−	+	+	−	−	−
Deficiencies of defects in thromboplastin formation: Prower	−	−	−	−	+	−	(+)	−	−	−	−	+	−	−	−
Deficiencies of defects in thromboplastin formation: Stuart	−	−	+	−	+	+	+	−	+	−	−	+	−	−	−
Afibrinogenæmia	−	−	+	±	+	+	−	−	−	−	−	−	+	−	−
Fibrolysins	−	±	−	±	−	−	±	−	−	−	−	−	±	+	−

\+ denotes an abnormal result, while − indicates a normal test.

AHG is synonymous with antihæmophilic globulin, or AHF; Xmas factor with PTC.; factor V with labile factor, proaccelerin, plasma accelerator globulin; and factor VII with stable factor, proconvertin and SPCA.

Fat Absorption

Of all techniques used, traditionally the fat balance has been the most reliable index of lipid absorption. Vitamin A absorption curves, chylomicron counts and fat tolerance tests have been advocated from time to time, but all these, as well as the fat balance, are exacting methods. Further, the fat balance is often a disagreeable chore for laboratory and nursing personnel. Adequate screening tests have long been sought, and methods using labelled fat now appear to fill this need.[9, 20, 63, 70, 75] These methods have been explored extensively in adults by using I^{131}-labelled triolein.[9, 63, 70] In principle, the labelled

TABLE 14. *Urinary Iodine Excretion in Normals and in Subjects with Malabsorption Syndrome after Lipiodol Ingestion*

SUBJECT	ML. LIPIODOL	IODINE IN THE URINE IN MG. PER CENT			
		Before	6 Hr.	12 Hr.	18 Hr.
		Normals			
M.F.	7.5	0.0	208	735	778
W.B.	6.0	0.0	165	177.7	52.8
D.B.	5.0	0.0	339.7	350.0	356.5
K.C.	5.0	0.0	480.9	710.0	549
E.C.	10.0	0.0	92.2	208.1	214.8
		Patients with Malabsorption Syndrome			
H.B.	10.0	3.0	15.6	54.0	20.8
N.B.	7.5	0.0	27.5	30.7	37.5
P.B.	7.0	8.8	82.0	45.2	32.2
S.R.	5.0	0.0	4.3	23.8	28.8
L.L.	5.0	0.0	0.0	0.0	0.0
J.B.	10.0	0.0	4.0	8.1	8.1
R.E.	5.0	0.0	24.9	62.6	35.9

triglyceride is either absorbed directly or hydrolysed and absorbed. The latter pathway depends upon the activity of pancreatic lipase. The blood level of I^{131} is an index of fat absorption, and, conversely, the I^{131} in the stool indicates the amount of labelled unabsorbed fat.[63] Reemstma *et al.*[61] have applied the method to the investigation of absorption in fibrocystic disease of the pancreas using I^{131}-labelled olive oil and I^{131}-labelled oleic acid and have shown a defect not only in lipolysis, but also in absorption. The defect in fatty acid absorption is not present in patients with pancreatic resection, fibrosis or tumour.

Methods for assessing absorption which utilize the estimation of I^{131} blood levels have a disadvantage in that the blood I^{131} concentration is dependent on several factors. The amount of labelled iodine in the plasma will depend on its absorption, intermediary metabolism, and excretion. At present all data would seem to correlate best with

absorption, excretory and intermediary metabolism being of lesser import.[63]

To circumvent the use of radio-active material in children and to develop a test that can be easily adapted to most laboratories, Delory, Israels and Jonasson[20] have modified the method of Silverman and Shirkey.[75] Lipiodol is used as the test material, and iodine estimations

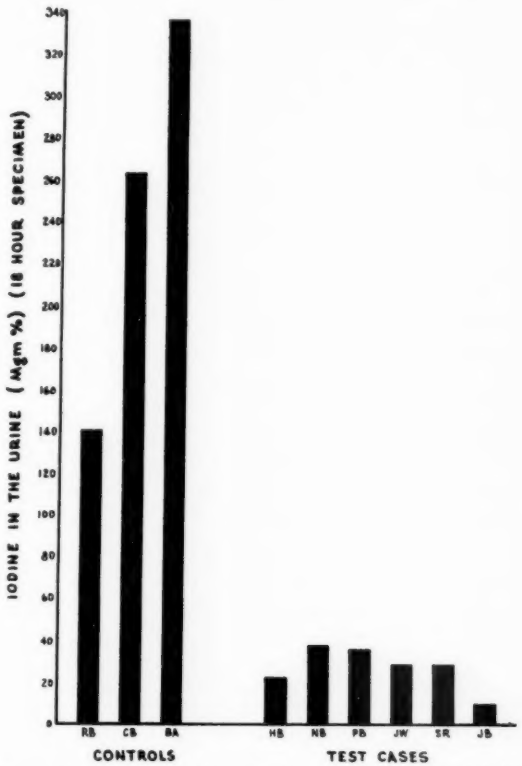

Fig. 16. Comparison of the maximum urinary concentration of iodine in normal subjects and in cases of malabsorption syndrome. The 3 normals are representative of 60 normals studied.

are done on specimens of urine taken at six, 12 and 18 hours after Lipiodol ingestion. The results of this test are shown in Table 14. There is a clear differentiation between the normal and abnormal values. In malabsorption syndrome we never find the value of iodine in the urine over 120 mg. per 100 ml. The bar graph in Figure 16 depicts the values in cases of fibrocystic disease as compared with normal values, and Table 15 shows the relation of the test to the fat balance.

TABLE 15. *Comparison of Fat Balance with Lipiodol Absorption Tests in Normal Subjects and in Cases of Malabsorption Syndrome*

SUBJECT	IODINE IN URINE BEFORE LIPIODOL	IODINE IN URINE AFTER LIPIODOL			AVERAGE DAILY %
		6 Hrs.	12 Hrs.	18 Hrs.	
Normals					
D.M.	0.0	154.2	361.7	288.1	91.5
B.L.	0.0	265.2	871.6	790.2	91.6
E.A.	0.0	18.0	204.0	205.6	97.6
G.F.	0.0	0.0	101.6	353.3	97.3
R.R.	0.0	36.3	171.9	238.7	97.2
Malabsorption Cases					
S.R.	0.0	0.0	3.9	12.6	71.6
M.R.	0.0	21.8	78.9	92.6	77.8
J.B.	0.0	4.0	8.1	8.1	4.0

This simple procedure is an adequate screening method for detecting poor fat absorption. An extension of the method using salivary iodine levels yields similar results.[38]

Sweat Chlorides

The discovery by Darling *et al.*[19] of the excessive secretion of sodium and chloride by exocrine glands in fibrocystic disease of the pancreas added a new approach to this disease and made its name even more suspect. The test using sweat has increased the diagnostic accuracy in this disease (99 out of 100 proved cases have a positive test[21]) and removed the necessity of passing a duodenal tube—a method yielding a significantly less clear result, subject to greater error, and of great inconvenience to the patient. Progress has been made from the exacting earlier methods involving the collection of sweat on gauze sponges, weighing, elution, and the measurement of the sodium and chloride[22, 23] to the simpler and more readily available test using agar plates,[73] and more recently the filter paper method of Webb and Geiger.[89] Of the methods in common use, the agar plate and the filter paper yield results which are usually diagnostic. These tests depend upon the precipitation of silver chloride in a medium of silver nitrate and potassium chromate. The chloride is derived from the abnormally high levels of this ion in the sweat of the patient. Photography of the plate or appending the filter paper to the chart leaves a permanent record of the test.

Preparation of the agar plates has been described by Shwachman.[73] Webb and Geiger's method[89] is even more simple. A piece of filter paper on which a drop of

2 per cent silver nitrate has been placed is grasped between the thumb and forefinger by the test subject. Ten per cent potassium chromate is then dropped on the filter paper, and if sweat chlorides are in excess amount, the thumbprint can be outlined as a light area on a dark background. The agar plate test of Shwachman[73] can also serve in the detection of persons heterozygous for the disease.

Quantitative evaluation of chlorides and sodium can be performed readily on samples of sweat collected in the following manner. The infant is placed in an incubator with humidity set at or above 50 per cent. The brow is washed clean with distilled water and dried. Hexadienol may be applied to the brow to promote sweating, and the incubator is turned up to 88° F. Usually within 35 minutes beads of sweat stand out on the forehead and can be harvested with a plastic spoon or a Wright's capsule. The chloride determination is done by the method of Schales and Schales.[65] This simple method of collection obviates weighing, plastic bags,[72] and the like, and we have found it remarkably reproducible and easy to carry out.

Salivary Chlorides

Salivary chloride values may be abnormal in fibrocystic disease of the pancreas.[47] Their estimation has, however, not proved to be a satisfactory diagnostic procedure in our hands.* The saliva collected by pledget likely represents the product of many salivary glands, and we have found it difficult to apply cups to the parotid ducts to get pure parotid secretion. Further, the overlap in values between normal and abnormal makes the test of doubtful value in some instances.[47] Originally the ease of collection of saliva was an important advantage of this method over the sweat test, but the newer methods of doing the sweat test and its greater diagnostic value make it the method of choice.

Mucoproteins in Duodenal Secretions

Mucoproteins in the duodenal secretions of fibrocystics differ chemically and physically from normals.[24] In fibrocystic disease the duodenal mucus is water-insoluble after precipitation with ethanol-benzene. The use of this finding as a clinical diagnostic test is not likely to supersede such an easy procedure as the sweat chloride.

Carbohydrate Absorption

The d-xylose absorption test as an index of carbohydrate absorption has been in use for some time. It has recently been reviewed by Benson *et al.*[10] Wolfish[94] reported on its value in infants in 1955. It has the advantage over glucose in not being altered by factors which affect plasma glucose levels such as hepatic, renal or endocrine influences.[10] It is a pure measure of carbohydrate absorption. The five-hour urinary excretion of this material is apparently a better test of absorption than blood estimation.[10] This makes the method technically

* S. Israels and E. Gourley: Unpublished data.

simple and obviates venipuncture. Perry* has found the test to be of value in detecting poor carbohydrate absorption in cœliac disease.

Protein Absorption

Standard methods using gelatin and glycine as test substances are satisfactory, and newer techniques have little advantage in the routine laboratory. Two new tests have been advocated. Lavick *et al.*[52] used I^{131}-labelled casein and measured the amount of this substance excreted in the stool. This has the disadvantage of using radio-active material. Gould and Shwachman[33] developed a test utilizing proline absorption that would appear to be a simple method of measuring hydrolysis of protein and absorption of this amino acid. The test in essence estimates serum proline levels two hours after the administration of a meal containing 15 per cent protein. The stated advantage of the test is the ease of proline estimation.

Gluten Sensitivity

The dramatic response of some cœliac patients to the gluten-free diet has led to the development of a test for gluten sensitivity. Weijers[90] and his associates found that gluten-sensitive subjects showed an unusual rise in serum glutamine after ingestion of gliadin. The difficulty in the test has been in the estimation of blood glutamine, since it is an exacting procedure. The therapeutic trial with a gluten-free diet is often rewarding in cases of suspected sensitivity. One patient of the authors gained 15 pounds in two months on such a diet, and the symptoms reappeared within six hours of reinstituting a regular diet.

LIVER FUNCTION TEST FOR BILIARY ATRESIA

Geppert[32] has devised a method for the diagnosis of biliary atresia by the use of I^{131}-labelled Rose Bengal. The failure of this dye to appear in the stools after intravenous injection apparently establishes the diagnosis of extrahepatic biliary atresia. The authors have used a similar principle utilizing bromsulfalein and examining for its presence in the stool.

URINE AND KIDNEY

TESTS FOR ABNORMAL URINARY CONSTITUENTS

Examination of the urine for abnormal substances was one of medicine's earliest laboratory procedures, yet each year newer diagnostic methods are added.

* W. Perry: Unpublished data.

Test for Urinary Glucose

The use of methods involving glucose oxidase is a boon to both the practicing physician and the diabetic. Detection of glycosuria is now a much simpler task, dispensing with test tubes, bottles, burners and tablets. The disadvantages are that the specificity of the method eliminates the possibility of picking up such non-glucose-reducing substances in the urine as galactose[1] and that the method is not quantitative. The latter fact limits its value in the management of the diabetic.*

Chromatographic Analysis for Amino Acids, Sugars and Steroids

Chromatographic methods using filter paper, starch, or columns of varied chemical content have been widely exploited in the identification of a number of substances in the urine. This technique, which made identification of amino acids in the urine a relatively easy procedure, has been the means of establishing aminoaciduria as a feature of many disorders.[37] Table 16 lists a variety of pædiatric diseases in which aminoaciduria is a prominent finding. Similar techniques are used for the identification of monosaccharides and are key tests in the diagnosis of galactosuria, fructosuria and pentosuria. Phosphoethanolamine, first identified by paper chromatography in hypophosphatasia, is now known to be present in the urine in scurvy, cœliac disease and hypothyroidism.[28] The separation by this means of urinary steroids has been of value in the diagnosis of aldosteronism[31] and the adrenogenital syndrome.[12]

Urinary Sediment

The examination of the elements of urinary sediment has been extended as a diagnostic method in recent years to include diseases beyond the kidney. Cytomegalic inclusion bodies in the cells of the urinary sediment are diagnostic of generalized cytomegalic inclusion disease. In addition, the virus associated with this disease may be cultured from such sediment.[91] The presence of metachromatic bodies in urinary sediment is diagnostic of metachromatic leucoencephalopathy in children, a diagnosis difficult to confirm by any other means.[5] Metachromatic granules can be seen *post mortem* in the cells of the renal tubules, and this likely is the source of the urinary material during life.

TESTS OF UNILATERAL RENAL FUNCTION IN HYPERTENSIVE DISEASE

Demonstrable unilateral renal disease associated with hypertension would seem an ideal situation for cure by removal of the affected

* S. Israels and E. Gourley: Unpublished data.

TABLE 16. *Amino Acid Content of Urine in Normal Infants and Adults, and in Some States of Aminoaciduria*

	NORMAL ADULT[37]	NORMAL INFANT[37]	PHENYLKE-TONURIA[37]	HEPATIC FAILURE[37]	CYSTIN-URIA[37]	FANCONI CHILD[37]	RICKETS[37]	MAPLE SUGAR URINE[92]	HARTNUP DISEASE[8]
Taurine	++++	0	+	++++	+	+	0	−	+++
Aspartic	+	+	0	++	0	0	+	−	−
Threonine	++	+	+	+++	+	++++	+++	0	−
Serine	++	++	−	++++	+	++++	+++	0	++++
Asparagine	++	0	0	+	+	++++	0	−	++++
Glutamic	+	+	+	+++	0	+	+	−	++++
Proline	+	0	0	+	0	++++	+	−	+
Glycine	++++	++	+++	++++	++++	++++	++++	−	+++
Alanine	++	0	+	0	0	++++	+++	0	++++
Cystine	+	+	0	++++	++++	+	+	+	+++
Valine	+	++	+	++	+	++++	+	++++	++++
Methionine	+	+	0	++	0	+	+	++++	−
Isoleucine	+	+	+	++	+	++++	+	++++	++++
Leucine	+	+	0	++	+	++++	++	++++	++++
Tyrosine	+	+	+	+++	+	++++	+	−	++++
Phenylalanine	+	+	+++	++	+	+++	+++	−	++++
Histidine	++++	++	++	++++	+	++++	+	−	++++
Tryptophane	+	0	+	++	0	0	0	−	++++
Ornithine	0	0	0	0	++++	++	+++	−	−
Lysine	+	+	+	++	++++	++++	0	−	+++
Arginine	0	+	0	++	++++	+	0	−	0
Ethanolamine	0	0	0	+++	0	0	0	−	−
Amino-isobutyric acid	0	0	0	++	0	+++	0	−	−

0 = None found in urine.
− = None recorded by author.
+ to ++++ = Quantitative expression of amounts excreted based on author's description.

kidney. These hopes have not often been realized, and only occasionally has one been able to reverse hypertension by removal of what appears to be a single diseased kidney.[78] To the present the results of unilateral nephrectomy have been unpredictable. Connor and his associates[17] have now developed a test by which, it is claimed, one can foretell the effect of nephrectomy on blood pressure. The test is based on the observations made by White[93] on the dog. He observed that urine from the ischæmic kidney was reduced in volume and sodium concentration. These findings in man have been noted by Connor and his group, and removal of the affected kidney has resulted in a cure of the associated hypertension.

RENAL BIOPSY

This technique has been widely used by Iversen and Brun[45] and has proved to be a rewarding method in elucidating pathological processes in many renal diseases. In addition, the method has cast some light on some types of renal disease hitherto unrecognized or poorly understood.[86] Muehrcke and his group used the biopsy for bacteriological culture as well as for histological examination.[59] The diagnostic possibilities of this procedure are only beginning to be exploited and should enhance the diagnostic potential of the clinician, now that the sorting of renal disease can be aided by histological examination. The technique is described in detail by Muehrcke *et al.*[59] and is relatively free of complications.

CHEMISTRY AND IMMUNOLOGY OF BLOOD AND SERUM

BLOOD GLUCOSE

The use of glucose oxidase in the determination of glucose gave hope of a rapid and accurate method of estimating blood glucose. This method to date does not appear to have any great advantage over the standard tests in use. Kits utilizing this method of analysis have been placed on the market, but in our hands have proved of limited value. This, however, has not been the finding of others.[43] One can see their use as an aid in the management of diabetic coma in smaller centres where technicians are not always available.

SERUM ENZYMES

There has long been an interest in serum enzyme levels in the diagnosis and prognosis of disease. Alkaline phosphatase, amylase, lipase and glucuronidase all have a place in the diagnostic laboratory. Glutamic oxaloacetic transaminase (SGOT) has been used in the

diagnosis and prognosis in myocardial damage as well as other diseases of muscle.[60] This enzyme, as well as glutamic pyruvic transaminase (SGPT), has been explored in the investigation of hepatic disease and in erythroblastosis.[50] Normal values for these tests are higher in the newborn period than in the adult (SGOT up to 120 units, SGPT up to 90 units). These values are apparently unaffected by erythroblastosis unless it is complicated by biliary obstruction.[52]

Serum aldolase[88] values have been used as an index of muscle destruction in muscular dystrophy. The test apparently has not the specificity claimed for it by Schapira.[66] The levels are high in hepatitis and in infectious mononucleosis.[74] Blanchaer and Chown[11] have used the measurement of serum lactic dehydrogenase as an index of continuing red cell destruction in erythroblastosis.

IMMUNOLOGICAL TECHNIQUES

This review will only refer briefly to these methods, since they are not commonly used laboratory procedures. Janeway and Gitlin[46] have more accurately defined the agammaglobulinæmias by using immunological methods, and Gitlin[30] has also by this means clarified the origin of the hyaline in hyaline membrane disease. The present methods of measuring gamma globulin by electrophoresis or salting out are not too satisfactory. Gitlin's procedure is more accurate and could be adapted for use in the routine laboratory.

Hodes[40] has added an important new method to the diagnosis of viral disease. The method used for identifying poliomyelitis depends on viral inactivation on filter paper strips saturated with specific antiserum. Methods of antibody detection using tanned red cells as an indicator promise to be a valuable adjunct in immunological diagnosis. It has already been adapted to the platelets in auto-immune thrombocytopenic purpura.[49]

The agglutination of Rhesus cells by the serum of a patient with infectious hepatitis has been reported[42] and, if confirmed, would be the first positive laboratory method of diagnosing this illness. The agglutination of sensitized bentonite particles has been reported by Bunim *et al.*[13] to be a simple and effective method in the diagnosis of rheumatoid disease. This test is attractive for its ease of conduct. As early rheumatoid arthritis is a difficult and important diagnosis to make, such a test should be of great value.

TESTS OF CHROMOSOMAL SEX

Moore and Barr[58] have developed a method of identifying chromosomal sex in interphase nuclei. This is a procedure that can be carried out by using a variety of different cells. In our own hospital Dr. Moore

prefers the oral smear. The test is invaluable in the diagnosis of adrenogenital syndrome and in some cases of gonadal dysgenesis and Kleinfelter's syndrome.[25] For a thorough discussion of the interpretation of chromosomal sex patterns the reader is referred to the excellent article of Donan and associates.[25] The application of nuclear sexing to amniotic fluid obtained prenatally has been the subject of a recent report.[64] It may be that this aspect of the test may have a clinical application in predicting before birth certain diseases which are sex-linked.

This has been a brief review of some recently popularized laboratory techniques as applied to pædiatric practice. The clinician has innumerable laboratory tests available to him. The skill required is to use them intelligently to solve the problem at hand.

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DIAGNOSIS AND MANAGEMENT OF SEX ANOMALIES

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The management of sex anomalies such as hermaphroditism has long been difficult and confused. Recently a laboratory procedure has been introduced which is of considerable value in the diagnosis, and consequently in the care, of these patients and of other errors of sex development. This procedure is a cytological test of chromosomal sex and, when used in conjunction with our recent knowledge of the chemistry and pharmacology of the sex hormones, makes the care of sex anomalous cases much simpler than heretofore. The aim of this paper is to outline the technique of cytological testing and to present a simplified method of care for these problem cases. Some of the present thoughts on their pathogenesis will be discussed briefly.

TESTS OF CHROMOSOMAL SEX

Several methods are available to test chromosomal sex. In principle, the procedures are based on the presence or absence of a special mass of chromatin, the sex chromatin, in the cell nuclei of a patient. Since the sex chromatin is present in the nuclei of all normal females that have been examined, and consistently absent in normal males, it seems to be a reliable guide to the sex of a person at a cellular level. More

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specifically, the sex chromatin is thought to represent heterochromatic portions of the two X-chromosomes of female cells. For reasons that are not entirely clear, the XY-sex chromosome complex of male cells fails to form a chromatin mass of appreciable size in intermitotic nuclei. The tests are useful in clinical diagnosis because the apparent sex is often at variance with the chromosomal sex in developmental sex anomalies. The following procedures are in current use.

Oral Mucosal Smear

This method was introduced by Moore and Barr[31] and Marberger *et al.*[27] It has proved to be reliable and is preferred over the others because of its simplicity. The smears are prepared by scraping the

Fig. 17.

Fig. 18.

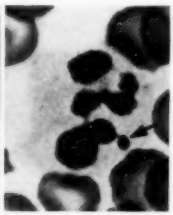

Fig. 19.

Fig. 17. Nucleus in an oral smear preparation from a chromosomal female, with the sex chromatin in its typical position against the nuclear membrane. Thionine stain. × 1600.

Fig. 18. Nuclei in epidermal spinous cells from a chromosomal female, with sex chromatin in each nucleus. Hematoxylin and eosin stain. × 1800.

Fig. 19. A neutrophile leucocyte with the accessory nuclear lobule that occurs in an average of 2 to 3 per cent of neutrophils of chromosomal females. Giemsa stain. × 1600.

mucosa of the cheek with the edge of a narrow metal spatula, transferring the material to an albuminized slide, fixing for 30 minutes in a 50:50 mixture of 95 per cent alcohol and ether, and staining with a basic dye such as thionine or cresylecht violet. The preparations are improved, through sharpening of nuclear detail and elimination of bacterial staining, by mild acid hydrolysis before staining as recommended by Klinger and Ludwig.[22] From 40 to 80 per cent of healthy nuclei, with smooth contours and finely particulate general chromatin, contain visible sex chromatin in chromosomal females (Fig. 17). The sex chromatin is usually planoconvex in outline or considerably flattened, and closely adherent to the inner surface of the nuclear membrane. It is lacking in smear preparations from chromosomal males. Variants of the method are the use of vaginal smears[5] or smears from urinary sediment.[9] However, oral smears are preferred for routine use.

Skin Biopsy Method

Introduced by Moore *et al.*,[32] this procedure has largely given way to the simpler and more rapid oral smear technique. The skin biopsy method involves obtaining a small specimen of skin from any location, fixation in a formol-acetic-alcohol mixture, and staining of sections 5 microns thick with hematoxylin and eosin and by the Feulgen method. Special care is required at all stages of the procedure to avoid nuclear shrinkage and other technical artifacts. The nuclei in the spinous layer show the typical characteristics of sex at the cellular level (Fig. 18).

Neutrophile Method

This procedure is based on a sexual dimorphism in the nuclei of neutrophile leucocytes that was described by Davidson and Smith.[6] In females a small proportion of neutrophils (2 to 3 per cent, on the average) have an accessory nuclear lobule that is lacking in neutrophils of males (Fig. 19). The accessory lobule is attached to a lobe of the nucleus by a filamentous connection and has to be distinguished from various nuclear appendages that occur in both sexes. It has been suggested that the accessory lobule contains the sex chromatin, but this is uncertain.[1] Although the blood film is as easy to obtain as the oral smear, the neutrophile method has the disadvantage of being rather tedious because of the large number of cells that have to be studied in some films for a reliable interpretation.

In order to minimize the possibility of a sex-reversed person becoming aware of his or her biological history, it is our practice to report preparations with female nuclei as "chromatin-positive" and preparations with male nuclei as "chromatin-negative," even though these terms leave much to be desired if they are interpreted in a literal sense.

RELATION OF SEX CHROMATIN TO SEX CHROMOSOMES

The sex chromatin of female cells is thought to be derived from certain regions of the two X-chromosomes that adhere to each other. These regions are said to be heterochromatic, which means that they remain condensed and deeply staining in the intermitotic nucleus, when euchromatic regions of the chromosomes are so altered physically from their metaphase state as to be unrecognizable. This interpretation, although probably correct, needs to be examined critically. In considering this matter, it may be recalled that the nuclear sexual dimorphism that forms the basis of tests of sex in clinical practice is a general property of human tissues[30] and the tissues of a number of mammalian species.[29]

The following lines of evidence strongly suggest that the sex chromatin of female cells is a chromosomal derivative and that it is related to the XX-sex chromosome complex.

1. The sex chromatin contains desoxyribose nucleic acid (DNA), as shown by its distinctly Feulgen-positive staining reaction. Nucleoli are Feulgen-negative, their nucleic acid being of the ribose type (RNA). Since DNA is the principal nucleic acid of the chromosomes, it seems that the sex chromatin must somehow be derived from them. In fact, Atkin and Doxey[2] have seen the sex chromatin as a densely staining chromosome region in early prophase in squash preparations of human cancer tissue.

2. The sex chromatin can be resolved into two components (resembling a diplococcus) in preparations of high technical quality when it is suitably oriented to the optical axis of the microscope. Smears or sections that have been subjected to mild acid hydrolysis and then stained with thionine, according to the method of Klinger and Ludwig,[22] are especially suitable for studying details of this sort. The bipartite state of the sex chromatin suggests that two homologous members of a pair of chromosomes are involved. Of the 24 (or 23[10]) pairs of chromosomes, the XX pair is the logical choice because the main distinction between the chromosome complement of males and females is the XY complex of the former and the XX complex of the latter. Further, the sex chromosomes are noteworthy in having accentuated heterochromatic properties, compared with the autosomes. This characteristic of the sex chromosomes has been subjected to closest scrutiny in male germ cells, but it has been demonstrated in somatic cells of insects by Geitler[11] and others. Even allowing for the small size of the Y-chromosome, one would expect nuclei of males to have a mass of sex chromatin that is at least half the size of the sex chromatin of female cells. That is not so, and the inconspicuousness of the sex chromatin in cells of males has not been adequately explained.

3. The study of chromocentres, or clumps of chromatin, in epidermal cell nuclei by Sachs and Danon[40] has a special bearing on the relation between sex chromatin and sex chromosomes. The nuclei of old spinous cells of females contained the typical bipartite sex chromatin, and a similar chromocentre was absent in old spinous cells of males. In the young spinous cells of females, on the other hand, there were frequently two chromocentres equal in size and located at some distance from each other. Similarly, there were frequently two chromocentres in young spinous cells of males, but one was smaller than the other. Sachs and Danon concluded that it was possible to identify X and Y chromocentres in young spinous cells. This refinement of the skin biopsy method forecasts the possibility of recognizing

unusual sex chromosome complexes (e.g., XO or XXY), should these occur in certain sex anomalies.

Segal and Nelson[41] suggested that the sex chromatin of female nuclei may be derived from regions that contain male-determining genes on a pair of autosomes. These regions might be genetically inert when exhibiting heterochromatic properties in the female, and genetically active when behaving in a euchromatic manner in the male. For various reasons this hypothesis seems to be less probable than the one relating the sex chromatin to the sex chromosomes themselves.

The tissue cells are exposed to abnormal levels of sex hormones in certain sex anomalies, either as an inherent factor in the developmental error or through the administration of sex hormones therapeutically. The tests of chromosomal sex would be unreliable were the sex chromatin readily influenced by hormonal factors, but the following lines of evidence show that it is a stable component of the nucleus.

(*a*) The sexual dimorphism in nuclear structure is present from early embryonic stages of development, even before gonadal differentiation, through the entire life span of the individual.[13] The constancy of nuclear structure from the early embryo to senility argues strongly against the sex chromatin being influenced by sex hormones or other endocrine factors.

(*b*) The imprint of sex on nuclei of the mature cat is not altered by gonadectomy in either sex shortly after birth or by administration of the contrary sex hormone to gonadectomized animals.*

(*c*) Nerve cell nuclei of the bovine freemartin contain typical female sex chromatin,[33] in accordance with Lillie's demonstration that the freemartin is a genetic female.[25] This shows that the hormone from the male twin that partially masculinizes its female co-twin has no recognizable influence on the sex chromatin.

(*d*) Nuclei have a typical female appearance in the adrenogenital syndrome in females, although their cells have been exposed to levels of an androgenic hormone that caused partial masculinization of the external genitalia.[3]

(*e*) Klinger[21] found that nuclei of maternal and fœtal portions of the placenta, although close to each other and bathed in the same fluids, were consistently female in cells of maternal origin and male or female in cells of fœtal origin, depending on the sex of the fœtus. He concluded that the presence or absence of sex chromatin did not result from extracellular influences.

The foregoing evidence amounts to virtual proof that the presence or absence of sex chromatin is a valid indication of the chromosomal sex of an individual, even though genetic, hormonal or other factors

* H. A. Lindsay: Unpublished data.

have caused varying degrees of sex reversal during embryological development.

TESTS OF CHROMOSOMAL SEX IN SEX ANOMALIES IN MAN

Clinical use of the tests of chromosomal sex has been mainly with respect to the various types of hermaphroditism and the various gonadal dysgeneses. There are hopeful signs that a new approach to the study of sex anomalies may lead to a better understanding of their relationship to each other.[15, 16, 18, 46]

Male Pseudohermaphroditism

This is a highly variable group, having in common the presence of testes, usually in the pelvis or inguinal canals. The degree of feminization of the internal and external genitals varies greatly from one patient to another. The most highly feminized subjects belong to the testicular feminization syndrome of Morris, a type of male pseudohermaphrodite with feminine secondary sex characteristics in whom primary amenorrhœa may be the only overt sign of sex reversal. From this extreme, patients have decreasing feminization of the genitals, culminating in the relatively masculine patient with hypospadias and bifid scrotum. There is a definite familial incidence, especially for the testicular feminization type of patient, and the study of pedigrees indicates that male pseudohermaphroditism stems from a recessive gene on an X-chromosome,[42] although this is probably an over-simplification, and more complex genetic mechanisms have been postulated.[46]

According to the former view, the recessive gene is transmitted through phenotypically normal females to half of their sons, who are affected, and half of their daughters, who are carriers of the trait. The genetic error appears to be responsible for a deficient elaboration of the masculinizing hormone or inductor of the fœtal testes which causes a defective masculinization of the reproductive system, as suggested by Jost.[20] The variations from one patient to another have been attributed to differences in the degree of hormonal failure on the part of the fœtal testes. These patients have a gonadal endocrine deficiency in common with patients with gonadal dysgenesis (Turner's syndrome, p. 386), who are chromosomal males, and it is not surprising that patients have been encountered who occupy a transitional position between the two syndromes so far as clinical findings are concerned.[16]

All male pseudohermaphrodites so far tested have been chromosomal males,[3, 7, 24, 34] in confirmation of the views of Jost as to their pathogenesis. The tests of chromosomal sex help to distinguish a male pseudohermaphrodite with moderate feminization of the genitals from a

female pseudohermaphrodite, and explain the cause of primary amenorrhœa in highly feminized male pseudohermaphrodites. Three such cases have been studied in Victoria Hospital, London, since the tests became available.

CASE I. M.J., aged 26 years, was first seen in 1954 with a history of being reared as a boy. At 8 years of age he had an abdominal exploration. At 11 years he was subjected to cystoscopy for monthly hæmaturia. At 14 years he had a bilateral mastectomy. At 15 years abdominal exploration was undertaken, and one testis was found. At 16 years a scrotal prosthesis was inserted. At this time suicide was attempted. At 24 years one testicle was removed from the abdomen, while a second was biopsied. At 25 years a female reconstruction was performed and an artificial vagina made. A brother had similar genitals. She desires work with a doctor or minister who will understand her problem. All procedures were carried out in different hospitals from coast to coast. Cells are chromatin-negative.

CASE II. B.C., aged 16 years, was admitted in April, 1954. The patient had been reared as a girl and had an enlarged clitoris which was removed at 9 years. The voice deepened at 12 to 13 years, and the patient began shaving. Examination revealed a male build, minimal breast development, female genitalia, 17-ketosteroids 16 mg. per 24 hours, cells chromatin-negative, and good periods on cyclical estrogens. Operation revealed well-developed testes, which were removed.

CASE III. J.C., aged 21 years, was admitted in January, 1956. The patient had been reared as a girl and showed good breast development on hormones. She married at 17 years. Examination revealed a heavy-boned female, female genitalia and pubic hair, 17-ketosteroids 17.5 mg. per 24 hours, cells chromatin-negative. She is a "sister" of B.C. (Case II).

The first case demonstrated the folly of changing the sex after early childhood, for this patient is now very emotionally disturbed. The other two, who were reared as females, had no problems beyond amenorrhœa and sterility.

Female Pseudohermaphroditism

DUE TO ADRENOCORTICAL HYPERFUNCTION. Abnormal androgen production by the adrenal cortex may have its onset before or after birth in either sex when due to hyperplasia or tumour. Before birth, bilateral hyperplasia is the rule, while from birth to puberty tumour is more common, and in later life either condition may apply. If the excessive androgen production occurs in a male, development will be accelerated along masculine lines, and sexual precocity is noted. The female fœtus undergoing androgenization develops abnormalities of the genital tract with a tendency to persistence of the urogenital sinus and clitoral hypertrophy. The genital anomaly may make difficult the assignment of the true sex, since it may be impossible to differentiate the condition from other types of sexual abnormality on the basis of physical examination alone. The gonadal status may be determined by establishing the presence or absence of sex chromatin as previously outlined, although the rare true hermaphrodite (p. 386) introduces a relatively

minor element of uncertainty. The diagnosis may then be supported by a determination of the urinary 17-ketosteroids after three to four weeks of age. These latter are normally less than 0.5 mg. per 24 hours during the first two to three years of life, but may be between 2 and 6 mg. per 24 hours in the presence of adrenocortical hyperplasia.

Untreated, the child is subjected to the virilizing and growth-promoting effect of excessive androgen production. Hirsutism, excessive muscular development, oily skin, acne, prominence of the laryngeal cartilage, coarsening of the voice and rapid growth with early epiphysial union and ultimate short stature are prominent features. The syndrome is progressive from birth in the congenital variety of the adrenogenital syndrome, while the male pseudohermaphrodite shows no progression of the condition until puberty.

In spite of excessive adrenal androgen production, about 25 per cent of infants with congenital adrenocortical hyperplasia have a deficiency of the electrolyte metabolic hormones. Sodium loss, potassium retention and an Addisonian crisis usually appear in these patients within the first few weeks of life. Irritability, failure to feed, vomiting, weight loss and circulatory collapse is the usual sequence of events if treatment is not initiated. This complication may be recognized more easily in the female, in whom the genital anomalies are clearly apparent, while the male infant with the same syndrome may exhibit only normal or slightly increased penile proportions. Occasionally the Addisonian complication may not appear until later in childhood during a period of added stress, such as trauma or intercurrent infection.

A variant of this syndrome has been described in which adrenal hyperplasia with virilization was accompanied by hypertension.[43]

In broad terms, the virilizing hyperplastic adrenals fail to produce adequate quantities of the hydrocortisone-like compounds, and a consequent increased production of ACTH from the pituitary occurs. This may cause excessive adrenocortical stimulation with excessive androgen production as the end-result. This aspect of the problem has recently been reviewed by Reifenstein.[39] The abnormal production of adrenal sex steroids suppresses gonadotrophin production by the anterior pituitary, and thus gonads fail to mature and function adequately. In a female, failure of estrogen production results in primary amenorrhœa and a lack of the usual secondary sex characteristics. In a male, androgen production is already excessive, and so full masculinization occurs, but the testes fail to function, and azoospermia and infertility usually follow unless therapy is given.

In those patients whose virilizing process begins after birth, adrenocortical tumour must be considered. Pyelograms or pre-sacral air insufflation may assist in the diagnosis and localization of an adrenal tumour. The urinary 17-ketosteroids often are much higher in the

presence of a tumour compared with that found in adrenal hyperplasia. If 50 to 100 mg. of cortisone are given daily by injection or by mouth, the 17-ketosteroid production of hyperplastic adrenals will decrease to near-normal values within seven to 10 days. This therapy usually causes little change if a tumour is present. The dose of cortisone may be reduced for younger children. A clear-cut response to cortisone is considered diagnostic of adrenocortical hyperplasia, and exploration of the adrenals is therefore not necessary. Failure to respond, however, indicates the presence of a tumour, and surgical investigation should be carried out. The following case histories are illustrative.

CASE IV. G.B. was seen in August, 1953, at the age of 14 months because of clitoral hypertrophy, swelling of the labia and some evidence of pubic hair growth. The parents felt that the clitoral and labial hypertrophy had been present since birth. The child was born at full term, weighed 9 pounds 3 ounces at birth, and had thrived well. The one sibling, a 12-year-old brother, was normal. The remainder of the family history was not contributory. Physical examination revealed a female infant, large for her age, weighing 18 pounds 15 ounces, and with abnormal genitalia as noted above. Under anæsthetic a rectal examination failed to reveal a pelvic mass. The vagina, urethra and cervix were in keeping with her age, and cystoscopy with retrograde pyelography revealed no unusual findings. Serum electrolytes were normal, and the urinary 17-ketosteroids were 5.5 mg. per 24 hours. The patient was given 6.25 mg. of cortisone by mouth twice daily, and the urinary 17-ketosteroids decreased from 5.5 to 1.3 mg. per 24 hours on the third day, rising to 2.6 mg. on the fourth and fifth days. Because the reliability of the cortisone suppression test was not well proved at that time, a surgical exploration of the adrenals was carried out. No evidence of tumour was found, and the infant was given 6.25 mg. of cortisone by mouth twice daily. Since that time the steroid therapy has been changed to hydrocortisone, and the dose has ranged from 20 to 30 mg. a day in divided doses, depending upon the level of urinary 17-ketosteroids. In general, these have been maintained at a level of less than 5 mg. per 24 hours, and now, 4 years after the institution of therapy, at the age of 5 years, the weight is 47 pounds 8 ounces, height 43 inches, and there has been no further growth of clitoris or pubic and axillary hair.

CASE V. B.S. was first seen in November, 1951, at the age of 7 years. She had undergone considerable increase in statural growth during the previous year and had axillary and pubic hair, deepening of the voice and clitoral hypertrophy of phallic proportions (Figs. 20, 21). Bone age was consistent with a chronological age of 16 years. The urinary 17-ketosteroids were reported as 16.6 mg. per 24 hours. Serum electrolytes were essentially normal. The hæmoglobin was 17.4 gm. per 100 ml. An intravenous pyelogram revealed evidence of a large, oval, soft tissue mass above the upper pole of the right kidney. An adrenal exploration was carried out, and an obvious tumour of the right adrenal was found and removed (Fig. 22). The left adrenal appeared to be normal in size and consistency. Pathologically, the tumour was an adrenocortical adenoma, considered to be benign histologically. The patient was given adrenocortical extract during the operative and immediate post-operative periods. The post-operative course was without incident.

Thirteen months later the urinary 17-ketosteroids were 5.2 mg. per 24 hours, hæmoglobin 16.8 gm., chest x-ray normal, and clinically she was doing well. Axillary and pubic hair still remained, and the clitoris was unchanged. Breast development had started. The child has undergone normal pubescence, menstruates normally, and continues to be clinically well at the age of 13 years.

CASE VI. T.B., a male patient, was born in January, 1949. The birth weight was 8 pounds 5½ ounces. No abnormality was noted at birth or during hospitalization at

Fig. 20. B.S., age 7 years. Androgenic adrenal tumour. Bone age 16 years. 17-ketosteroids, 16.6 mg. per day.

Fig. 21. Virilizing effect on genitalia.

the age of 6 months for an upper respiratory tract infection. He developed rapidly during the next 3 years, and in October, 1952, was admitted for investigation of sexual precocity. At this time it was noted that the testes were small, and that there was exaggerated penile development, axillary and pubic hair growth and excessive muscularity (Fig. 23). His stature, bone age and dentition corresponded to that of a 6-year-old. The 17-ketosteroids were 9.3 mg. per 24 hours, but a cortisone suppression test was not carried out at that time. An intravenous pyelogram failed to reveal any abnormality. A second 17-ketosteroid estimation was reported as 19.1 mg. per 24 hours. An adrenal exploration was carried out, and no evidence of adrenal tumour

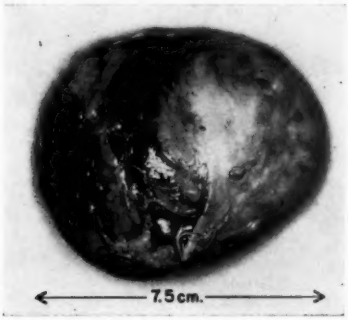

Fig. 22. Tumour removed at operation.

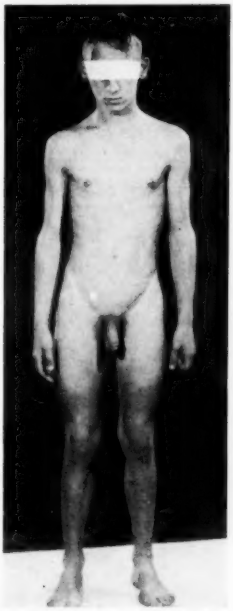

Fig. 23. T.B., age 8½ years. Congenital adrenal hyperplasia in a male. 17-ketosteroids, 22.1 mg. per day.

was found. An attempt was made to institute cortisone therapy, but through lack of co-operation this was discontinued. The patient was first seen by one of us at 8 7/12 years (July, 1957), at which time his measurements were as follows: height, 65¾ inches; pubis to floor, 30¾ inches; pubis to crown, 35 inches; span, 62½ inches. He was muscular, and had axillary and pubic hair growth, some prominence of the laryngeal cartilage and definite penile development. The testes were juvenile in size. The 17-ketosteroids were reported as 22.1 mg. per 24 hours, and on cortisone therapy (75 mg. a day in divided doses) the values decreased to 4.2 mg. per 24 hours by the sixth day. Since that time he has been maintained on 25 mg. of cortisone a day in

divided doses, and the 17-ketosteroid values have been reported as 5.0 mg. per 24 hours.

WITH NORMAL ADRENAL FUNCTION. These patients are extremely rare and are chromatin-positive with external genitalia of an intersexual type. There is no progression of secondary sexual characteristics until puberty, when feminization tends to occur. None of these cases has come under our supervision.

True Hermaphroditism

True hermaphrodites with ovotestes or one of each type of gonad are also rare, although not as uncommon as female pseudo-hermaphrodites with normal adrenal function. They usually are chromatin-positive by a ratio of 3:1. Their secondary sexual characteristics are unpredictable. These can readily be confused with the pseudohermaphrodites. Surgical exploration will confirm the diagnosis.

Gonadal Dysgenesis

The application of tests of chromosomal sex to patients with gonadal dysgenesis (Turner's syndrome) was of special significance, since it led to a correlation between certain experimental observations in lower mammals and a particularly puzzling sex anomaly. The condition was known formerly as "ovarian" agenesis, but the word "gonadal" had to be substituted for "ovarian" in the light of recent findings. "Dysgenesis," rather than "agenesis," is favoured by some because the gonads are rudimentary rather than absent. The main clinical findings are as follows:

These patients are essentially females who lack definitive ovarian tissue. The gonads are represented by streaks of connective tissue in the broad ligaments that may contain remnants of the mesonephric ducts and tubules, but no truly gonadal elements. The connective tissue simulates ovarian stroma, and there may be aggregates of cells resembling ovarian hilar cells. The remainder of the genital system is definitely female, although there is usually some degree of hypoplasia. Short stature is the rule in the classic syndrome, and a valuable hint to the possibility of gonadal dysgenesis in the prepuberal period. The absence of functional gonads leads to sexual infantilism after puberty, and an increased excretion of pituitary gonadotrophin after the age of 10 years, unless there is estrogen substitution therapy. Inconstant findings, in order of decreasing frequency, are cubitus valgus, webbing of the neck, skeletal anomalies involving the thorax and mandible especially, coarctation of the aorta and subnormal mentality. The presence of coarctation of the aorta in this list is especially significant because it rarely occurs in females.

The foregoing description refers to the classic syndrome. Variants have been described, especially patients with normal stature, and, in fact, no congenital defect other than the gonadal.[18] A few patients have been described with hypertrophy of the clitoris. There appear to be rare patients who form a transition between gonadal dysgenesis in its usual form and the male pseudohermaphrodite.[16]

Before 1950 there was a gradual accumulation of experimental evidence indicating that the embryonal testis has an essential role in the maturation of the reproductive system. The most conclusive experiments involved gonadectomy of young embryos. Studies of this sort were done by Jost[19] on the rabbit and by Raynaud and Frilley[38] on the mouse. Removal or destruction of embryonal ovaries had little effect on the subsequent development of the female reproductive system. However, when embryonal testes were removed sufficiently early, the reproductive system developed in the female direction, in spite of the genetic maleness of the embryo. It appears that the reproductive system generally has an inherent tendency to feminize and that a hormone or inductor elaborated by the fœtal testes is required to effect masculinization. Jost[20] suggested that the "ovarian" agenesis or Turner's syndrome type of patient might be Nature's counterpart, in man, of his experiments on lower animals. This suggestion was confirmed, soon after the cytological methods of chromosomal sex detection were introduced, by Polani *et al.*,[37] Wilkins *et al.*[44] and Lima *et al.*[26] They all found cases of so-called ovarian agenesis with male nuclei which were apparently instances of male-to-female sex reversal due to the absence of embryonal testes and their masculinizing hormone. The name was changed to gonadal agenesis or gonadal dysgenesis. Later studies showed that about 80 per cent of patients with gonadal dysgenesis are chromosomal males. [3, 7, 16, 34]

While the feminization of these patients has a likely explanation in experimental work, the cause of the gonadal dysgenesis and concurrent anomalies is not known. Klotz *et al.*[23] described two sisters with gonadal dysgenesis whose parents were first cousins, and referred to three other instances in which the abnormality occurred in two siblings arising from a consanguineous marriage. They make the interesting observation that in some instances shortness of stature is inherited on the maternal side through several generations, and that eventually gonadal dysgenesis may occur along with the shortness of stature, which marks the end of the line for this particular hereditary sequence. Hoffenberg and Jackson[18] have proposed a more detailed genetic hypothesis. They postulate three closely related genes on the same chromosome: one for the gonadal defect, another for shortness of stature, and a third, or a gene complex, for the various other anomalies. When all three factors are inherited and have a high degree of penetrance, the classic syndrome results; the effect of one or two of the three genes would result in apparently related syndromes. Detailed records of family histories need to be accumulated.

Ætiological factors other than genetic have been suggested, such as a noxious agent of maternal origin,[16] and fertilization of an overripe ovum with subsequent failure of the primordial germ cells to reach the gonadal ridges from extra-embryonic entoderm.[45]

Dysgenesis of the Seminiferous Tubules

Until recent years tubular dysgenesis (Klinefelter's syndrome) was seldom diagnosed until the patient was beyond the "pædiatric age group." Azoospermia, gynæcomastia, small testes associated with hyalinization of the seminiferous tubules and persisting clumps of Leydig cells, mild to moderate degrees of eunuchoidism and elevation of urinary gonadotrophin characterize Klinefelter's syndrome as originally described. Later papers indicated that gynæcomastia and eunuchoidism were not necessarily present.

More recently it has been shown that a proportion of patients with Klinefelter's syndrome have chromatin-positive nuclei. Apart from this and the possible existence of gynæcomastia, these patients exhibit no clinical evidence of feminization and therefore represent an almost complete female-to-male sex reversal.[15, 34, 36, 41] Although abnormally small testes provide a clue, it has been difficult to diagnose this group before pubescence. Now with the confirmatory evidence supplied by sex chromatin studies, a patient with abnormally small testes may be shown to belong to the Klinefelter group at an earlier age.

Pathological examination of the testes of such patients reveals varying degrees of fibrosis and hyalinization of the seminiferous tubules associated with azoospermia. Many of the seminiferous tubules are represented by hyaline masses that are smaller than normal tubules, and a small lumen may be present. However, there are none of the cells characteristic of the epithelium of normal seminiferous tubules within these hyalinized masses. Other tubules exhibit a severe fibrotic thickening of the tunica propria and contain epithelial cells whose nature cannot be easily decided. Sertoli cells are recognizable in tubules with less severe fibrosis, and there is occasional evidence of spermatogenesis. The testes contain a normal number of Leydig cells arranged in large clumps.

Available evidence indicates that the development of abnormal testis-like gonads rather than ovaries, in an embryo whose cells contain two X-chromosomes, is the result of an error in the sex-determining genes. Masculinization of the embryo is presumably brought about by the endocrine activity of the abundant Leydig cells, thus leading to a male individual with a female XX-sex chromosome complex.

Other patients with essentially the same clinical appearance have chromatin-negative nuclei. In general, the tubular changes previously described are less prominent, and the Leydig cells are more dispersed. Endocrine function of this latter group is similar to that of the group with chromatin-positive nuclei. Because of differences in the criteria for selection of patients for study, a considerable variation is noted in the percentage of chromatin-positive to chromatin-negative patients

who may be grouped under the heading of Klinefelter's syndrome. Nelson,[34] for example, found that 70 of 88 patients exhibited chromatin-positive nuclei, while 18 were chromatin-negative. Grumbach *et al.*[15] found that of 32 hypogonadal males classified as having seminiferous tubule dysgenesis on clinical and pathological grounds, only nine had chromatin-positive nuclei. This discrepancy will probably continue until our knowledge of testicular pathology is further advanced. The following case history illustrates the type of patient with female-to-male sex reversal.

Fig. 24. L.T., age 31 years. Klinefelter's syndrome. Cells chromatin-positive. 17-ketosteroids, 5.8 mg. per day.

Case VII. F.T., a 31-year-old man, was seen because of presumed sterility (Fig. 24). Birth and early development were considered to have been normal. Adolescence was delayed, and he did not shave until the age of 28. There was no history of orchitis or injury to the genital area.

The patient was of slim, eunuchoid build, weighing 125 pounds. His height was 65½ inches, span 68½ inches, pubis to floor 34 inches, pubis to crown 31½ inches. The voice was fairly well modulated, although the laryngeal cartilage was not prominent. There was no gynæcomastia or prominence of the breast areas. Beard growth was slight, and minimal hair growth was present on limbs and body. The pubic hair was sparse and gynæcoid in distribution. Axillary hair was also sparse. The hair of the head was thick, without recession at the temples. The penis was well within normal limits of size. The testes were about one-third normal size, rather soft but tender. They were situated in a normal scrotum. The ejaculate was 2.5 cc. in volume and contained no spermatozoa. The urinary excretion of 17-ketosteroids was low (5.8 and

4.9 mg. per 24 hours) on two occasions. Urinary gonadotrophins were within the normal range (+2 to −10 rat uterine units). The nuclei in a skin biopsy specimen and oral smear were typically chromatin-positive, and the incidence of female-type neutrophils was well within the range for normal females. It has not been possible to obtain testicular biopsy material from this patient, but other cases have been reported more completely.[4, 38]

CLINICAL MANAGEMENT

Thus the academic approach to sex anomalies has shed considerable light on these bizarre clinical problems, and the clinical management is now more clearly understood.

Male Pseudohermaphroditism and True Hermaphroditism

The following general rules apply to the management of male pseudohermaphrodites and the rare true hermaphrodite:

1. When any doubt exists as to the external sexual characteristics, an oral smear should be taken at once. If this shows chromatin-positive cells, then 17-ketosteroid and electrolyte studies must be done to eliminate the possibility of female pseudohermaphroditism with adrenocortical hyperfunction. This is so readily treated with corticosteroids that it must never be overlooked.

Similarly, when abnormal secondary sexual characteristics appear at puberty, an oral smear should be studied at once. If there is a conflict between the chromosomal sex and the sex of rearing, great care should be taken to avoid the patient's learning this because of the psychological trauma which may result.

2. The external genitals should be closely studied, and the parents should be advised to rear the child in the sex which more closely corresponds to the genitals. This decision is influenced in part by the difficulty of extensive plastic surgery involved in phallic reconstruction. It is much simpler to construct an artificial vagina than a penis. Therefore, if any doubt exists, it is preferable to rear the child as a female. Further support is given to this policy by the greater acceptability by society of a "tomboy" girl than a "feminine" boy.[17] Girls are also more inclined to modesty and privacy, a fact which makes any genital aberrations more easily concealed.

3. Management of the internal genital duct system should be considered at an early age, preferably under one and one-half years. In most instances urogenital orifices should be investigated radiologically and by cystoscope. This should be followed by exploratory pelvic laparotomy to demonstrate the internal genital system. Gross and Meeker[14] have suggested that no removal of tissue beyond gonadal biopsy should be performed at this time and wisely counsel a cautious consideration of all findings before removal of gonads or internal

genital ducts. If such a decision is reached, operation should be carried out before two years of age by preference. It is imperative that the patient's management be definitive before schooling is commenced. Early gonad removal in the male pseudohermaphrodite with border-line genitals, who is to be raised as a female, will avoid the embarrassment of possible masculinization at puberty. In the older child the appearance of secondary sex characteristics opposed to the sex of upbringing is an absolute indication for removal of gonads. The suitable secondary sexual characteristics can be produced by oral hormone therapy.

4. Much has been written concerning the psychological trauma in these cases.[8, 28] Certainly, M.J. (case I) was greatly disturbed by the vacillating course followed by the various medical attendants. It seems vital that the permanent sex of upbringing be decided before the age of 18 months. Psychologists have shown that erotic interests are more related to the sex of upbringing than to chromosomal sex or hormonal factors.[28] Therefore, when one sees a hermaphrodite after two years of age, it is unwise to attempt any sexual version, and all efforts should be made to establish the child in the previously chosen sex role.

5. In children reared as females, with female internal duct system, hormonal therapy is usually necessary as puberty approaches, in order that they may develop as near to normality as possible. Stilbestrol is given in 0.5- to 1-mg. doses daily. When adolescence is reached, anhydrohydroxyprogesterone, 10 to 30 mg. a day, is given in the third week of a cycle, and then the estrogen and progesterone are discontinued. The estrogen is restarted in one week's time at the start of a new cycle. This usually produces satisfactory menstrual bleeding when normal internal sex ducts exist. When the female internal duct system is rudimentary, cyclical estrogen and progesterone are not necessary. Daily estrogen is necessary for complete feminization.

6. In children reared as males, methyl testosterone is given by oral linguets in doses of 10 to 30 mg. a day, which allows a fairly normal growth. This should, of course, not be started until near adolescence.

Congenital Adrenocortical Hyperplasia

Patients with congenital adrenocortical hyperplasia producing female pseudohermaphroditism must be investigated as thoroughly as possible so that their exact endocrine and physical status is understood. If this investigation is carried out during infancy, a clear-cut line of management may be followed as a rule. These patients will hardly have had time to develop any psychological reversal, and since it is usually simpler and more effective to carry them in the role of a female, this is usually the course which is taken. Cortisone by mouth or injection suppresses ACTH production, and consequently there is a decrease

in the adrenocortical sex steroid production. This prevents further virilization, and gonadotrophin is released by the anterior pituitary when the patient approaches puberty. This hormone stimulates the gonads to function, and a normal pubescence may follow. One such patient who was started on treatment at age 28 underwent a full and normal pubescence at this time, became pregnant and was delivered of a living normal female by Cæsarean section.

The dose of cortisone required varies considerably from patient to patient, but in the younger age groups 25 to 50 mg. of cortisone daily, by divided doses, taken orally, will generally be adequate. Although there is some advantage in using injections of cortisone, owing to its more even release from the intramuscular depots thus established, results of treatment have been satisfactory with oral medication, and the convenience to the patient is of considerable importance.

Surgical removal of the clitoris, preferably before the age of two years, should be carried out if it is of phallic proportions or sufficiently hypertrophied as to be a likely source of future embarrassment.

The therapy must be continued indefinitely, since withdrawal of the medication is followed by a return of the virilizing process, even after years of medication. Since these patients have some deficiency of corticoid production, the administered cortisone is, at least in part, replacement therapy, and side effects from its use are less apparent than one might ordinarily expect. However, since there is suppression of intrinsic adrenal function during this treatment, these patients might require extra cortisone during periods of exceptional stress, such as surgery or severe infection.

Treatment of males with this syndrome is essentially the same. Apart from the sexual precocity, excessive muscular development and statural growth, there will be suppression of gonadotrophin production, resulting in atrophic, underdeveloped testes. Cortisone therapy brings about a correction of this endocrine situation, allowing release of pituitary gonadotrophin and maturation of the testes with eventual spermatogenesis.

Those patients with adrenocortical hyperplasia accompanied by virilism and hypertension may also be treated by cortisone. It is interesting that the hypertension may also be corrected by this therapy.

The adrenogenital syndrome, when accompanied by a deficiency of the salt and water metabolic hormones, requires a more complex replacement therapeutic program. Daily administration of desoxycorticosterone acetate (DCA) plus cortisone is usually sufficient to correct the metabolic error. When the daily requirement of DCA is determined, it is then possible to calculate the amount required and administer the medication in the form of subcutaneous pellets. As an alternative, it should be possible to treat these patients with 9-alpha-

fluorohydrocortisone by oral tablet. This new preparation is extremely potent in its sodium- and chloride-retaining properties. Many of these patients recover some salt and water control after one year of therapy.

Gonadal Dysgenesis

Patients with gonadal dysgenesis (Turner's syndrome) in the pædiatric age group require treatment mainly from the psychological point of view. Early diagnosis is imperative in order to allow intelligent counselling. Estrogenic therapy should not be started until puberty, when stilbestrol should be given as outlined above. Interrupted therapy with the addition of progesterone may be added at the age of adolescence when an internal genital duct system exists (p. 386).

Dysgenesis of Seminiferous Tubules

Patients with dysgenesis of the seminiferous tubules (Klinefelter's syndrome) may require replacement androgen therapy. The sex chromatin studies previously described present the possibility of diagnosing this condition at an earlier age than formerly, and it may therefore be possible to initiate androgen therapy at the age of puberty rather than wait until later in life. With close observation and careful management it may be possible to prevent many of the eunuchoid characteristics and the early climacteric, which occur in a proportion of these patients. Though they will always be sterile, modifications of psychological disturbances and improved virilization could thus be accomplished. Androgen therapy is given as above.

SUMMARY

Recent progress in the study of human sex anomalies, including the introduction of tests of chromosomal sex, has verified animal experiments that demonstrated the vital rôle of an androgenic hormone from the fœtal testis in effecting normal masculinization of the male fœtus. A deficiency of this hormone causes a male-to-female sex reversal (gonadal dysgenesis, or Turner's syndrome, and male pseudohermaphroditism); the elaboration of this hormone by abnormal gonads causes a female-to-male sex reversal (seminiferous tubule dysgenesis, or Klinefelter's syndrome).

The tests of chromosomal sex are particularly useful clinically as an aid to the diagnosis of adrenocortical hyperplasia in female infants, gonadal dysgenesis in childhood, the testicular feminization syndrome during and after adolescence and the syndrome of seminiferous tubule dysgenesis. The tests are to be regarded only as aids to differential diagnosis.

A decision as to the more appropriate sex for the patient has to be based on the anatomy of the external genitals, the hormonal therapy available for the particular syndrome (especially cortisone for the adrenogenital syndrome) and, after infancy, on the sex of rearing up to the time the patient is first seen. With early, accurate diagnosis and careful management it is possible to direct a patient with a developmental sex anomaly toward a reasonably normal life, when the alternative might well have been an existence of intolerable misery.

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ALDOSTERONE IN EXPERIMENTAL AND CLINICAL MEDICINE

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The aim of this article is to discuss some aspects of the physiology of aldosterone, with particular reference to man. The discovery of this hormone by Simpson and Tait has stimulated so much work in many fields of research that an attempt to take all of it into account would be beyond the scope and the purpose of this article. Readers wishing to acquire further information on this subject are referred to the excellent reviews of Gaunt, Renzi and Chart[26] and of Luetscher[44] and to the first Symposium on Aldosterone, held in Geneva in 1957.[87]

THE FINDING AND ISOLATION OF ALDOSTERONE IN ADRENAL EXTRACTS AND BODY FLUIDS

During the past few years a new approach to the problem of the salt-retaining hormone of the adrenal cortex became available with the development of new and sensitive biological assays.[16, 18, 72] The use of one of these assays, all of which are based on the urinary excretion of sodium, or sodium and potassium, by adrenalectomized animals, led Deming and Luetscher[16] in 1950 to report the presence of a sodium-retaining factor in the crude lipid fraction of urine from œdematous patients. One year later Chart *et al.*[11] showed that similar urinary extracts from toxæmia of pregnancy were also highly potent in promoting sodium retention in adrenalectomized rats.

In 1952 Simpson and Tait, by means of a sensitive bio-assay[42] and of the new chromatographic methods of steroid separation proposed by Burton, Zaffaroni and Keutman[8] and by Bush,[9] discovered the presence of strong sodium-retaining activity in one specific chromatographic fraction of hog adrenal extracts.[88] The same substance was found in dog adrenal vein blood and in monkey adrenal perfusate.[76] This substance was separated by the same authors from the other known cortical hormones[73, 75] and obtained in crystalline form.[77, 78] The structure of the compound was established by means of chemical degradation by Simpson and Tait in collaboration with Wettstein, Neher, von Euw, Schindler and Reichstein in 1954.[79] It proved to be the 18-aldehyde of corticosterone, since referred to as aldosterone. In 1955 Wettstein[96] and his group succeeded in synthesizing the hormone.

Meanwhile the detection of a sodium-retaining factor in human urine was confirmed by the work of different groups of workers and extended to include different pathological conditions (McCall and Singer,[53] Singer and Wener,[82] Venning *et al.*[94]). The conclusive step in proving the identity of this factor with aldosterone was taken when Luetscher, Neher and Wettstein crystallized this hormone from nephrotic urine.[50]

SECRETION AND METABOLISM OF ALDOSTERONE

At present, and as the result of numerous investigations, aldosterone is considered by far the most potent electrolyte-regulating steroid of the mammalian adrenal cortex. Direct proof that the hormone is elaborated by the zona glomerulosa of beef and rat adrenal has recently been provided.[1, 29] Preliminary results of Tait[86] obtained by the incubation of different layers of the human adrenal cortex *in vitro* strongly suggest the same site of origin within the human adrenal cortex.

There is no general agreement regarding the rôle of different steroids in the pathway of aldosterone biosynthesis. In beef adrenal homogenates (^{14}C)-desoxycorticosterone was shown to yield (^{14}C)-aldosterone;[34] in perfusion of beef adrenals progesterone led to a greater amount of aldosterone formation than corticosterone, whereas desoxycorticosterone was ineffective in this respect.[69]

The secretion of aldosterone in the adrenal vein blood of rats,[81] dogs[23] and monkeys[76] has been recognized and its presence detected in pooled peripheral human blood.[74] The results of human studies with (16-^{3}H) aldosterone indicate that its half-life in peripheral blood is from three to five times shorter than that of (4-^{14}C) hydrocortisone.[2] This suggests that aldosterone is metabolized more rapidly than hydrocortisone. The concentration of the active hormone in blood is not much greater than 0.03 microgram per 100 ml. of plasma in subjects receiving a normal sodium intake. Such a concentration precludes the practical measurement of the biologically active hormone in blood by available chemical or physicochemical methods. The hormone is present in plasma in two forms, the free biologically active steroid, and a glucuronide conjugate, probably tetrahydro-aldosterone.

The rate of production of aldosterone by the adrenals of two normal subjects was calculated to be around 180 micrograms per day,[2] a value which agrees closely with the dose of 150 to 200 micrograms reported necessary to maintain electrolyte balance in Addison's disease. Like most corticosteroids, aldosterone is excreted in human urine as a free steroid which, under normal conditions, is present in minute amounts; as conjugate(s) as yet unidentified, but from which the free hormone can be recovered under special conditions of acid or β-glucuronidase hydrolysis, and as metabolites among which one is suspected to be tetra-

hydro-aldosterone.[87] Further proof of the presence of aldosterone in human urine is found in its recent isolation from cardiac failure,[51] normal pregnancy* and post-operative urines.[43]

EFFECT OF ALDOSTERONE ON ELECTROLYTE METABOLISM

Aldosterone has been shown to promote a positive sodium balance, and to maintain normal values of serum sodium in adrenalectomized dogs.[85] The administration of the hormone to patients with adrenal insufficiency is promptly followed by improvement of the clinical condition, as evidenced by an improved hydration, a rise of blood pressure toward normal, a retention of sodium and chloride and a less marked increase in potassium excretion.[35, 55, 57, 65, 91, 97] In certain studies fading of pigmentation and amelioration of the glucose tolerance curve have been noted.[55, 57, 65]

The daily maintenance dose in Addisonians varies between 150 and 200 micrograms. The hormone is effective when given orally. From these observations it has been generally recognized that aldosterone is about 20 to 30 times more potent than desoxycorticosterone in its sodium-retaining effect.[57] At this dose aldosterone does not promote excessive sodium and water retention. However, when 400 and 800 micrograms a day were administered to Addisonians, the development of mild œdema of the ankles and face was noticed.[71] It should be remembered that these doses correspond to the sodium-retaining potency of at least 8 and 16 mg. of DOCA a day respectively.

Aldosterone depresses sodium and increases potassium concentration in human saliva.[35] Simpson and Tait established that aldosterone given orally decreases the salivary sodium-potassium ratio in normals as well as in Addisonians. A quantitative correlation was found between the value of the sodium-potassium ratio and doses of aldosterone of 10 to 80 micrograms.[75] Further demonstration of the relation of aldosterone to sodium metabolism has been provided by Luetscher, who disclosed a striking correlation between urinary aldosterone and urinary concentration of sodium in such conditions as nephrosis, cardiac failure and cirrhosis of the liver.[48]

The first investigators felt that, in contrast to the action on sodium metabolism, aldosterone had a less striking rôle in the regulation of potassium. Desaulles reported that in acute experiments in rats aldosterone was only five times as active as desoxycorticosterone in promoting potassium excretion.[17] Swingle, by maintaining adrenalectomized dogs on small doses of aldosterone (1.5 to 3.1 micrograms a day per dog), was able to dissociate the action of the hormone on the serum sodium, which was maintained at a normal level, from that on serum potassium, which rose to a concentration of 5 to 8 mEq. per liter.[85] The qualitative difference between aldosterone and desoxycorticosterone acetate on potassium metabolism is further exemplified by the

* J. Genest: Personal communication.

observation of Gross.[31a] This author showed that during maintenance experiments in adrenalectomized dogs the substitution of aldosterone (50 micrograms a day) for desoxycorticosterone acetate (0.7 mg. a day), in doses which in his experience are of equivalent long-term maintenance potency, resulted in a decrease in urinary and an increase in serum potassium concentration. After a few days the plasma potassium reverted to normal. During the period of withdrawal of steroid administration, resumption of maintenance doses of DOCA led to a greater loss of potassium in the urine than did replacement with aldosterone. Furthermore, if the dose of aldosterone was raised twentyfold (1000 micrograms per day per dog), there was no definite increase in plasma sodium, nor decrease in plasma potassium, and no symptoms similar to those of DOCA overdosage.

Most of the studies performed in Addisonians as well as in normal subjects disclose only a slight effect of aldosterone on potassium balance over a wide range of dosage, varying between the maintenance dose of 150 micrograms per day in Addisonians to the dose of 1 mg. per day in normal subjects. In these studies the positive sodium balance which is practically always observed was accompanied by less notable changes in potassium excretion.[35, 57, 65] Similar findings are reported by Ward in rheumatoid arthritis[97] with doses of the hormone between 200 and 800 micrograms per day. In none of these studies was the serum potassium concentration noticeably affected.

However, the fact that up to the present the action of aldosterone on sodium metabolism has proved to be much more easily observed than its action on potassium should not overshadow the importance of an interrelationship between aldosterone and potassium. Singer[81] has shown that the secretion of aldosterone in the adrenal vein blood of normal rats is reduced by more than 90 per cent if the animal is submitted to a potassium-deficient diet. This observation has been confirmed in human subjects who presented only traces of aldosterone in their urine when receiving a potassium-deficient diet.[33] Also prominent features of primary aldosteronism (Conn's syndrome), whether due to adrenal tumour or hyperplasia, are a low serum potassium concentration, great loss of potassium in the urine and a general state of potassium depletion, proved by a decreased intracellular concentration of potassium in muscle.[13]

MECHANISMS INVOLVED IN THE SECRETION AND URINARY EXCRETION OF ALDOSTERONE

The physiological control of aldosterone production remains at present a much debated problem. It is generally accepted that, in man, the secretion of aldosterone is not primarily controlled by ACTH. This fact is substantiated by the observation that the urinary output of aldosterone has been found within the normal range in a number of patients presenting clinical symptoms of panhypopituitarism.[90, 92] How-

ever, a moderate to marked increase of urinary aldosterone has been repeatedly noted in human subjects receiving ACTH.[5, 40, 60, 62, 92] Compared to the stimulation of 17-ketosteroids and 17-hydroxycorticosteroids by ACTH, the increase of aldosterone is usually of smaller magnitude and of short duration. In most cases the excretion of the hormone falls to normal levels or even below when the administration of ACTH is continued. Since a slight but consistent effect of ACTH on aldosterone secretion has also been observed under conditions *in vitro*,[31, 70] it is difficult to dismiss the possibility of a direct effect of ACTH on aldosterone output. Observations have been presented which seem to indicate that the stimulating action of ACTH on aldosterone output is more strikingly demonstrable in subjects submitted to low sodium intake.[40, 90] Under these conditions the increased aldosterone output which characterizes low sodium intake (see below) is further enhanced by ACTH. Similarly, the increase of aldosterone excretion accompanied by sodium retention and diuresis, which follows withdrawal of Pitressin in normal subjects, is of a higher magnitude when ACTH is injected during this period.[60] In an attempt to explain this phenomenon Muller *et al.*[62] have advanced the hypothesis that the stimulating action of ACTH on aldosterone secretion is conditioned by fluctuations of the extra-cellular volume. A decrease of extra-cellular fluid volume would act synergistically with ACTH to increase aldosterone secretion, whereas an expansion of this volume would inhibit aldosterone release and therefore antagonize the ACTH effect. The short-lasting action of ACTH on aldosterone production observed by a number of authors might be explained by the extra-cellular sodium and water retention often noticed during ACTH therapy.

Monkey and human growth hormone injected into one patient suffering from panhypopituitarism has been observed by Beck *et al.*[6] to increase the urinary output of aldosterone by almost fourfold and sevenfold respectively. This finding was recently confirmed in a second patient.[7] The available data do not disclose whether the observed effect is due to a specific or an indirect effect of growth hormone on aldosterone excretion or to some contaminant present in the hormonal preparations used. These observations, together with experimental findings on dogs[67] and rats[81] which demonstrate a substantial decrease of aldosterone in the adrenal venous blood after hypophysectomy, tend to show that the pituitary may play a rôle in the control of aldosterone secretion.

The results of a number of investigations could be interpreted to show that the secretion of aldosterone is directly dependent upon variation of the potassium and/or the sodium pool. Luetscher[46] and his group established that the urinary output of aldosterone increases approximately fivefold in normal subjects on a low sodium intake (11

mEq. of sodium a day for seven days). This finding represented the first experimental proof in human subjects that a specific adrenal hormone is directly involved in the adjustment to sodium deprivation. The same observation has been made under conditions of extra-renal loss of sodium such as occurs in profuse sweating.[61] Low sodium intake, whether or not associated with extra-renal sodium loss, results in an increased rate of production of the hormone. This is exemplified by the finding of increased aldosterone content of the adrenal vein blood of rats subjected to sodium deprivation* and by an increase in the plasma concentration of the hormone in one subject depleted of sodium by sweating and restricted sodium intake.[2] In this subject the calculated rates of production by the adrenal (780 micrograms a day) showed an increase of more than fourfold compared to normal controls. Since the original observations of Luetscher it has been repeatedly demonstrated that restriction in sodium intake markedly increases the output of aldosterone.[61, 63, 90] Conversely, intake of a large quantity of sodium in a sodium-depleted subject will cause a fall in aldosterone output.[5, 63] On the other hand, potassium loading in dogs[38] as well as in man[3, 21] has been shown to promote increase in urinary output of aldosterone which was not entirely explained by the loss of sodium ordinarily induced by a potassium load. In fact, in sodium-depleted subjects, when the loss of sodium in the urine caused by a potassium load is replaced by simultaneous administration of this ion, a rise of aldosterone is nevertheless observed.[3] In rats[81] and in man[33] restricted potassium intake leads to a decreased aldosterone output in the adrenal vein blood and in urine respectively.

The fact that the variations of aldosterone output observed under these conditions are not accompanied by significant changes in 17-ketosteroids or 17-hydroxysteroids is in agreement with the hypothesis of Swan,[84] later substantiated by the experiment of Dean and Greep[15] on rats, according to which the secretion of the adrenal salt-retaining hormone, unlike that of other corticoids, was controlled by changes in electrolyte metabolism. However, clinical observations soon pointed out that variations in aldosterone output could not be solely related to electrolyte intake and that under certain experimental conditions the fluctuations of the hormone were better correlated with changes in body fluid volume than with serum sodium levels or with sodium balance. The elevated urinary output of aldosterone induced by low salt diet in man is depressed by expansion of the body fluid by means of over-hydration and Pitressin injections.[5, 59, 61] In this condition the output of aldosterone falls in spite of decreased serum sodium concentration and decreased total osmolarity. On the other hand, dehydration induced in diabetes insipidus by withdrawal of Pitressin, or in normal

* B. Singer: Personal communication.

subjects by restriction of water intake, produces an increase of aldosterone output in the presence of a decided rise of serum sodium concentration and total osmolarity.[5, 30] Inversely, the increased aldosterone output promoted by sodium restriction can be lowered by ingestion of large quantities of water.[58, 61]

It has also been pointed out that the infusion of hypertonic saline solution[5] or the ingestion of a large quantity of sodium[58, 61] into salt-depleted subjects lowers aldosterone excretion by an increase of extracellular fluid at the expense of a simultaneous contraction of intracellular fluid. This concept is strengthened when the observed decrease of aldosterone is not accompanied by significant changes in total body weight. Further analysis of the volume-regulating theory indicates that within the extra-cellular space the rôle of the intravascular volume might be of primary importance, since withdrawal of blood, immediately followed by replacement of volume by saline solution, produces a rise in aldosterone output; whereas immediate replacement of the intravascular volume by re-infusion of red blood cells and salt-poor albumin induces a fall in the urinary output of the hormone.[3]

The increasing importance accorded the hypothalamus in the control of endocrine functions had led for some time to the suspicion that the central nervous system might also participate in the regulation of electrolyte metabolism. In fact, hypothalamic lesions were shown by Lewy *et al.*[39] to produce hypernatræmia.

Recent work of Farrell and his group suggests the possibility that the secretion of aldosterone is regulated by a neurohumoral mechanism, largely independent of the adenohypophysis. Whereas hypophysectomized dogs secreted aldosterone at the rate of 66 per cent of normal controls,[67] decerebrate dogs showed a reduction to about 25 per cent of the normal.[66] After decortication the level of aldosterone was not affected. From this finding it was concluded that a neurohumoral aldosterone-regulating centre might be located within the thalamic-hypothalamic area. The existence of this centre was recently substantiated by the demonstration that extracts of beef diencephalon infused intravenously into decerebrate dogs brought back the secretion of aldosterone to normal.[22] In these experiments diencephalon extract also stimulated the rate of hydrocortisone secretion, but to a less extent.

At present it is evident that aldosterone is by far the most important steroid regulator of electrolyte metabolism in man. Under physiological conditions this control is achieved by minute amounts of the hormone in the circulating blood (about 0.015 microgram per 100 ml. of whole blood). The mechanism of secretion of aldosterone offers a complex picture in which hormonal factors and changes in electrolytes and in body fluid distribution are involved and possibly interrelated in ways as yet ill defined. As a pure hypothesis one might suggest that certain specific areas of the central nervous system are particularly sensitive to changes in intravascular volume to which they react by the release of a humoral factor controlling the rate of aldosterone secretion. If that is so, such a phenomenon would be broadly comparable to the

regulation of antidiuretic hormone secretion, by fluctuations in extracellular fluid osmolarity.

CLINICAL ASPECTS

The clinical syndromes which at present are known to be associated with hyperfunction or hypofunction of aldosterone are listed in Table 17. It is possible that any or all of these may be encountered in

TABLE 17. *Clinical Conditions Associated with Hyperfunction or Hypofunction of Aldosterone*

I. Clinical conditions associated with over-production of aldosterone
  A. Aldosteronism due to adrenal adenoma or bilateral hyperplasia (Conn's syndrome)
  B. Diseases complicated by œdema and sodium retention
    1. Nephrosis
    2. Cardiac failure
    3. Cirrhosis with ascites
    4. Idiopathic œdema
    5. Idiopathic hypoproteinæmia
  C. Diseases and clinical conditions uncomplicated by œdema
    1. Dehydration and sodium loss or restriction
    2. Familial periodic paralysis
    3. Sodium-losing nephritis
    4. Essential and malignant hypertension
    5. Congenital adrenal hyperplasia of the salt-losing type
  D. Clinical states in which excessive aldosterone and 17-hydroxycorticoid production co-exist
    1. After administration of ACTH
    2. After air encephalography
    3. Emotional stress
    4. Post-operative period
    5. Pregnancy
    6. Cushing's syndrome
    7. Adrenal cortical carcinoma
II. Clinical conditions associated with underproduction of aldosterone
  A. Isolated aldosterone lack
  B. Total adrenalectomy
  C. Addison's disease
  D. Acute adrenal insufficiency

children, not excepting pregnancy, which in the sexually precocious female child can occur at an early age. However, owing to the rarity of most of these conditions and to the difficulty of measuring aldosterone, well-documented information concerning mineralo-corticoid function, especially in children, is limited.

CLINICAL CONDITIONS ASSOCIATED WITH OVER-PRODUCTION OF ALDOSTERONE

Aldosteronism Due to Adrenal Adenoma or Bilateral Hyperplasia (Conn's Syndrome)

Previous to Conn's[12] description of the syndrome of primary aldosteronism in 1954 at least one case, which in retrospect appears to have

been an example of the syndrome, had been described in the literature under the heading of "potassium-losing nephritis."[20] The clinical manifestations include periodic attacks of weakness and paralysis—between which the patient may feel quite well—intermittent paræsthesias and tetany, polydipsia and polyuria, hypertension and absence of œdema. Associated with these are low serum potassium and somewhat elevated serum sodium concentrations, alkalosis and a dilute, protein-containing, alkaline urine whose specific gravity is not increased after Pitressin or fluid restriction. Potassium loss in the urine is severe, and the resulting negative balance can be overcome only by a high potassium intake. There is no evidence of Cushing's syndrome; 17-ketosteroid and 17-hydroxycorticoid excretions are normal. The urinary excretion of aldosterone may be as high as 26 times the normal value. However, this increase may not be a constant feature of the syndrome, since normal or even low urinary values have been reported. It has been suggested that these low values are a consequence of long-standing potassium depletion.[25]

Exploration of the adrenals may reveal either cortical adenoma or bilateral hyperplasia. After surgical removal of the tumour or subtotal adrenalectomy the abnormal manifestations regress unless the disease has been too long established and irreversible renal damage has occurred. Biopsies of the kidney made at operation have shown changes in the tubules characteristic of severe potassium deficiency, as well as generalized arteriolosclerosis.

Over 40 cases of the syndrome have been described in adults, and it has been recognized occasionally in children. Kretchmer *et al.*[36] recently reported a typical case in a nine-year-old boy whose hypertension of 210/150 was discovered during an annual health examination. The child had had polyuria and polydipsia since infancy. He showed hypokalæmia, alkalosis, a persistently low urinary specific gravity and an elevated excretion of aldosterone (27 micrograms a day). Urinary 17-hydroxycorticoids and 17-ketosteroids were normal. When explored surgically, both adrenals were found to be hyperplastic, and all but 10 per cent of one adrenal gland was removed. After operation the patient showed significant clinical and laboratory improvement. Genest* has measured the urinary aldosterone in a 10-year-old child† with proved primary aldosteronism secondary to bilateral adrenal hyperplasia, and found it to be 27 micrograms a day (normal adult range 1.5 to 9.5 micrograms a day). Van Buchem *et al.*[92] described a 17-year-old boy with polyuria and polydipsia, low fixed urinary specific gravity, a serum potassium of 1.7 and 2.5 mEq., blood pressure fluctuating between 220/150 and 195/125, and high urinary excretions of

* J. Genest: Personal communication.

† Patient of Dr. Bernard Therien, Henry Ford Hospital, Detroit.

aldosterone. This patient did not complain of weakness, and there was no alkalosis. At operation no tumour was found, and subtotal adrenalectomy was carried out. After operation both the blood pressure and the serum potassium returned gradually to normal.

Foye and Feichtmeir[24] reported the case of a man in whom the signs and symptoms of Conn's syndrome had been present for only six to eight months. There were no signs of Cushing's disease, the 17-ketosteroids were normal, but the ketogenic steroids, determined by the Norymberski method, were elevated. An adrenal tumour was found and removed, after which there was a remission of all signs and symptoms for three months. Recurrence of the original abnormality was accompanied by pathologically elevated excretions of 17-ketosteroids and corticoids, as well as of aldosterone. At autopsy widely scattered tumour metastases were found, and the opposite adrenal was atrophic.

It will be seen from the foregoing that typical Conn's syndrome may arise from benign adrenal adenoma, bilateral adrenal hyperplasia or, more rarely, adrenal cortical carcinoma. In the last situation signs of over-activity of other adrenal cortical hormones will probably be found.

Diseases Complicated by Œdema and Sodium Retention

In 1949 Deming and Luetscher,[16] who were interested in the problem of why œdematous patients excrete minimal amounts of sodium in their urine, perfected a bio-assay method for the detection of "sodium-retaining activity" in human urine. Extracts made from the urine of certain patients with œdema (nephrotics and patients with cardiac failure) were found to produce sodium retention in adrenalectomized rats, whereas those from patients with other diseases and from normal controls were not. The salt-active factor concerned was thought to originate in the adrenal, since it was present only in lipid extracts of urine. These authors proceeded to investigate nephrotics while they were receiving cortisone[47] and ACTH[49]. They observed that the sodium-retaining activity of the urine increased for the first two to three days of ACTH therapy in certain patients, but diminished after about 10 days, and in all patients disappeared during diuresis, whether this occurred while hormone was being administered or after it had been discontinued. Diuresis and the concomitant disappearance of sodium-retaining factor were always accompanied by urinary loss of large amounts of sodium. Moreover, when diuresis failed to occur, the sodium-retaining activity remained high. A striking reduction in sodium-retaining activity was also apparent during diuresis when the latter followed the intravenous injection of albumin, indicating that

the low or absent sodium-retaining activity observed during diuresis was not dependent on a state of adrenal hypofunction, such as might follow withdrawal of ACTH or cortisone. As previously mentioned, this salt-active material was subsequently found to be aldosterone.

McCall and Singer[53] confirmed the presence of a sodium-retaining factor in urine from *nephrotic* children. They also demonstrated that although sodium-retaining activity decreased when diuresis occurred under continuous ACTH administration, the urinary formaldehydrogenic corticoids remained high. Hence it appeared that the adrenal activities represented by the two types of excretion products functioned independently of one another. More recently Singer,[80] studying experimental nephrosis in the rat, has found in adrenal vein blood of immature rats made nephrotic by daily injections of an aminonucleoside of puromycin, a higher aldosterone content than in normal controls. This finding suggests that in the nephrotic syndrome there is not only increased urinary excretion, but also actually an increased rate of production of aldosterone by the adrenals.

In *cardiac failure* with œdema[16, 82, 100] and in *cirrhosis with ascites*[10, 58] a high urinary content of sodium-retaining substances is frequently observed. After removal of ascitic fluid in cirrhotics a further increase of urinary aldosterone has been noticed.[4, 58] It has been suggested that this increase represents an attempt of the adrenal to compensate for the lowering of plasma volume resulting from the foregoing procedure.[58] After administration of aldosterone to cirrhotic patients 15 per cent of the hormone was reported to be recovered from the urine, whereas only 3 to 4 per cent was recovered after administration to normal subjects. This finding lends support to the view that damaged liver tissue is unable to inactivate the hormone to the same extent as normal liver tissue. This may be one of the factors contributing to secondary aldosteronism in cirrhosis.[99]

Mach *et al.*[54] have reported the finding of increased aldosterone output in patients with *idiopathic œdema*. These patients, generally women of middle age, tend to suffer œdema especially during stress, when they retain sodium and excrete abnormal amounts of aldosterone. Their serum proteins are normal, and the patients respond well to low sodium intake. One such patient was reported to accumulate œdema whenever her salt intake was in excess of 5 gm. a day. Another patient when subjected to sodium loading (10 gm. of sodium chloride a day for three days) excreted only 10 per cent of the load, whereas ingestion of large quantities of water was followed by sodium diuresis and temporary fall in urinary aldosterone.[54]

In *idiopathic hypoproteinæmia* elevated aldosterone excretion has also been noted. Bartter[3] showed that the intravenous administration of salt-poor human albumin to a woman suffering from this disease

resulted in a fall in aldosterone excretion through expansion of the intravascular space. There was also an accompanying salt and water diuresis and loss of weight. No reports on studies of children with any of the foregoing conditions have been found in the literature.

The cause(s) of the œdema in the foregoing conditions remain ill defined. But whatever the mechanisms concerned, excessive aldosterone function appears to be secondary to the underlying disease process, since it disappears when the disease itself is improved.

Diseases and Clinical States Uncomplicated by Œdema

As previously mentioned, it has been repeatedly shown that *restriction of sodium intake,* water deprivation and consequent *dehydration,* severe sweating, a high potassium intake and an increase in the serum concentration of potassium are important stimuli to increased aldosterone excretion. The level of serum sodium in itself appears to have little effect on aldosterone activity. From these observations it might be inferred that in sudden dehydration, such as that produced by rapid water loss from the bowel, aldosterone production is stimulated with a resulting increase in potassium excretion. When diarrhœa and dehydration have existed for any length of time, however, the lowered serum potassium concentration due to loss of this ion in stool and urine may tend to limit or even depress mineralocorticoid activity.[25]

The pathophysiology of *familial periodic paralysis* has been studied by Conn *et al.*[14] These authors found that atttacks of paralysis are preceded by greatly increased aldosterone excretion, while urinary ketosteroids and corticoids remain normal. They suggest that a possible "defect in the extra-adrenal mechanism which regulates adrenal secretion of aldosterone" is an important abnormality in this disease.

A patient with *sodium-losing nephritis,* whose urinary aldosterone excretions were measured by Luetscher, was dehydrated and had high aldosterone excretion while receiving a normal intake of sodium. When large amounts of sodium were ingested, hydration was improved and mineralo-corticoid function became normal. Thorn[89] points out that in this patient there was evidence of long-standing secondary aldosteronism, confirmed also by the decreased sodium-potassium ratio of the saliva, but that, because of his renal disease, retention of sodium could not be effected. The absence of hypertension in the patient is attributed by this author to lack of salt retention.

In an investigation of adults with *essential and malignant hypertension* Genest[27, 28] noted that relatively larger amounts of aldosterone were excreted by these patients than by normal subjects. A study of essential hypertension in a child has recently been made by Slater

et al.,[83] who carried out numerous investigations on a four-year-old boy over a period of two years. He presented none of the typical signs of Conn's syndrome. Extensive renal function studies failed to reveal primary renal disease, and there were no funduscopic changes. Aldosterone excretion, which in a control child of the same age was less than 1 microgram a day, was (in this case) 12 micrograms a day. Complete adrenalectomy was performed in two stages. After removal of one adrenal there was a temporary decrease in blood pressure and in aldosterone excretion. Both then returned to the former high level. After the second adrenalectomy, when the patient was receiving suitable substitution therapy, the blood pressure returned to normal.

Patients with *congenital adrenal hyperplasia of the salt-losing type* have been widely studied from the point of view of their mineralocorticoid function with rather conflicting results. Such patients suffer from repeated crises of the Addisonian type, and because it is known that in this disease the adrenal is unable to produce hydrocortisone in adequate amounts, it was first considered that the production of aldosterone might also be inadequate. However, aldosterone has repeatedly been found in the urine of these patients.[28, *] Prader *et al.*[64] found some increase in aldosterone excretion in two salt-losing infants, and a greater increase in an older child who had formerly been a salt loser. Of two adults with congenital adrenal hyperplasia studied by them, neither of whom had had salt-losing tendencies, the aldosterone was greatly increased in one. It has been suggested that in this syndrome the adrenal may elaborate hormones which produce salt excretion and that, to compensate for this, aldosterone may be produced in increased amounts. The salt loss in one such patient was not preventable by the administration of 300 micrograms of aldosterone daily.[44]

Clinical States in Which Excessive Aldosterone and 17-Hydrocorticoid Production Co-exist

It has been previously mentioned that the *injection of ACTH* produces a definite increase in aldosterone excretion as well as of other corticoids, although the increase of the former is only transitory. It is interesting to relate these observations with the findings of Lieberman and Luetscher,[41] who, investigating a group of patients subjected to *air encephalography*, found that an increase occurred in both mineralo-corticoid and hydrocortisone excretions which was similar to that seen following the administration of ACTH.

Increased aldosterone output has been reported to occur in certain types of *stress*. Lamson *et al.*[37] found an increase in aldosterone ex-

* J. A. Luetscher, Jr.: Personal communication.

cretion in patients with anxiety neurosis, results confirmed by Genest.[28] Venning, Dyrenfurth and Beck[94] showed that students writing examinations excreted significantly higher amounts of aldosterone than were eliminated under normal conditions. It was observed that in some patients an increase in 17-hydroxycorticoids also occurred.

During the early *post-operative period* Llaurado[42] observed the association of decreased sodium excretion and increased potassium excretion with an increase of sodium-retaining activity in the urine, and it is known that other corticoids are excreted in increased amounts for some days following surgical procedures.

Although it has been recognized for a number of years that both 17-hydroxycorticoids and biologically active corticoids are excreted in greatly increased amounts in *pregnancy*, it is only recently that Venning has also shown that the excretion of aldosterone is higher than normal during that period.[96] After delivery all urinary excretions fall abruptly to normal. Rinsler and Rigby[68] have recently suggested that the high level of aldosterone excretion in normal pregnancy may be part of a homeostatic reaction which counteracts the loss of sodium from the extra-cellular fluid into the maternal cells and fœtal tissues.

Cushing's syndrome is considered to be due to over-production by the adrenal of hydrocortisone and cortisone, hormones which predominantly affect carbohydrate and protein metabolism. However, an elevated serum sodium value, a hypokalæmic, hypochloræmic alkalosis, hypertension and muscular weakness are frequently important manifestations of the cushingoid state. It is therefore of interest that Genest[28] found high quantities of urinary aldosterone in a patient with Cushing's syndrome who showed hypertension and electrolyte abnormalities, but normal amounts of aldosterone in a 12-year-old girl with typical Cushing's syndrome in whom electrolyte metabolism was not disturbed.*

As mentioned previously, *adrenal cortical carcinoma*, which is usually manifested clinically as either Cushing's syndrome or the adrenogenital syndrome, may in the early stages present the signs and symptoms of Conn's syndrome alone. As the disease progresses, changes related to over-activity of all panels of the adrenal will appear.

CLINICAL CONDITIONS ASSOCIATED WITH UNDERPRODUCTION OF ALDOSTERONE

Isolated aldosterone lack in a patient whose production of other adrenal corticoids is normal has not been described until recently. Hudson *et al.*[32] studied an adult patient in whom episodes of complete heart block and cardiac standstill were associated with hyperpotassæmia.

* J. Genest: Personal communication.

During the period of study serum potassium levels as high as 8.9 mEq. per liter were observed. Adrenal glucocorticoid and androgenic functions were not disturbed, as attested by the normal ketosteroid and 17-hydroxycorticoid excretion and by other tests. The urinary aldosterone was low on a normal sodium intake and remained low when dietary sodium was restricted and the patient was stimulated by ACTH—an abnormal response indicating the inability of the adrenal to release aldosterone following stimuli usually effective in that respect. It was demonstrated, moreover, that the renal tubules were capable of responding to administered desoxycorticosterone acetate in a normal manner, i.e., with sodium retention and potassium excretion, findings which eliminated the kidney as a primary cause of the electrolyte disturbance.

In fully developed *Addison's disease*, and after *complete adrenalectomy*, aldosterone is absent from the urine.[45] Nevertheless rare patients are encountered with typical pigmentation and weakness, but without hypotension, who have no measurable 17-hydroxycorticoids in plasma or urine, but whose serum electrolytes are normally maintained. In such patients some aldosterone is excreted in the urine.* One of us[52] has studied two siblings aged five and nine years who fall into this group. These children were investigated because of poor appetite, weakness, pigmentation, and occasional bouts of abdominal pain and fever. There was no hypotension, and serum electrolytes were repeatedly within normal limits. In both children urinary corticoids, 17-ketosteroids and plasma corticoids were too low to be measurable, nor was an increase noted following 48 hours' stimulation with ACTH. Urinary aldosterone was present, though in low amounts, less than 1 microgram and 1.8 micrograms daily being excreted by each child respectively.†

In *acute adrenal insufficiency* it is likely that aldosterone production by the adrenal is low or entirely lacking. This syndrome is not rare in infants and young children during epidemics of meningococcal infection.

The limited amounts of aldosterone which up to the present have been available for clinical and therapeutic trial preclude any extensive discussion of its usefulness as a therapeutic agent. Nevertheless the relative absence of toxicity of the hormone in doses higher than those required for maintenance of adrenal-insufficient patients, and its oral effectiveness, make it likely that aldosterone may prove to be the ideal electrolyte-regulating steroid for the control of adrenal insufficiency. The therapeutic effectiveness of the hormone in conditions such as shock remains to be investigated.

* J. C. Beck: Personal communication.

† Kindly measured for us by Dr. E. H. Venning.

SUMMARY

1. Recent findings pertinent to the metabolism, the physiological action and the control of aldosterone secretion have been presented.

2. The clinical conditions in which aldosterone has been shown to be involved have been outlined, with particular reference to pædiatrics.

3. An attempt was made to present these clinical findings in the light of what is presently known of the mechanisms regulating the secretion and excretion of aldosterone.

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THE DIAGNOSIS AND MANAGEMENT OF THE VARIOUS TYPES OF RICKETS

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In the years following the suggestion that sunlight would prevent rickets[34] and the subsequent researches that culminated in the isolation of vitamin D[3, 31, 32, 45] there was a dramatic reduction in the incidence of rickets throughout the civilized world. Since that time the incidence of the disease has continued to fall, largely as a result of improvement in social and economic conditions, and of progress in the fields of public health and education. To-day, except in a few areas, vitamin D deficiency is no longer an important problem in pædiatrics.

Gratifying as has been this improvement, children with rickets still appear. In some a deficient intake of vitamin D is obvious, and the rickets heals rapidly on initiation of standard vitamin D therapy. There remains, however, a heterogeneous group of rachitic children in whom a history of vitamin deficiency cannot be elicited, and in whom active rickets persists despite the administration of conventional doses of vitamin D.

It is the purpose of this paper to outline an approach to the differential diagnosis of the various types of rickets met in medical and surgical practice, and to discuss certain present concepts concerning the management and prognosis of each type.

DEFINITION OF THE TERM "RICKETS"

Rickets may be defined as a generalized lesion of bone characterized by a failure of calcium salts to be deposited promptly in bone matrix

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TABLE 18. *Classification of Rickets*

	TYPE	ÆTIOLOGY	DESIGNATION PREFERRED BY AUTHORS	OTHER DESIGNATIONS FOR THE SYNDROME	NO. OF CASES H.S.C. 1946–55
Responsive to usual therapeutic doses of vitamin D.	I *Vitamin D deficiency*				
		i. Dietary deficiency of vitamin D	Vitamin D deficiency rickets	Rickets, classical rickets, infantile rickets, simple rickets, deficiency rickets.	70
		ii. Defective absorption of vitamin D and calcium due to steatorrhœa		Cœliac rickets.	
	II *Chronic renal insufficiency with secondary hyperparathyroidism.* (Chronic pyelonephritis, chronic glomerulonephritis, congenital renal abnormalities, late stage of types III, A, iii, iv, B, i)		Pannephritic osteodystrophy	Renal rickets, renal osteodystrophy, rickets due to glomerular insufficiency, glomerular rickets.	6
	III *Renal tubular insufficiency*				
		A. Renal tubular insufficiency resulting in phosphate depletion			
		i. Defective reabsorption of phosphate (± glucose)	Hypophosphatæmic vitamin D-refractory rickets of the simple type	Vitamin D-resistant rickets (with hypophosphatæmia), primary vitamin D-refractory rickets, tubular rickets, endogenous rickets, late rickets, rachitis tarda, phosphate diabetes, Milkman's syndrome (adult), idiopathic osteomalacia (adult).	14

'Resistant' to usual doses of vitamin D

ii. Defective reabsorption of phosphate, glucose, many amino-acids (± protein)	Hypophosphatæmic vitamin D-refractory rickets with aminoaciduria	Fanconi syndrome, Debré-deToni-Fanconi syndrome, nephrotic glycosuric dwarfism with hypophosphatæmic rickets, amindiabetes.	2
iii. Defective reabsorption of phosphate, glucose, many aminoacids, protein (± water), with defective conservation of fixed base	Hypophosphatæmic vitamin D-refractory rickets with aminoaciduria and acidosis		0
iv. Generalized defect in cystine metabolism, with (? secondary) defective tubular reabsorption of phosphate, glucose, many amino-acids, protein, fixed base (± water)	Cystine storage disease with vitamin D-refractory rickets	Fanconi syndrome, Debré-deToni-Fanconi syndrome, Lignac's disease, Lignac-Fanconi syndrome, cystinosis, cystinuria with rickets.	4
v. Defective reabsorption of phosphate, glycine and fixed base	Hypophosphatæmic vitamin D-refractory rickets with hyperglycinuria		0
vi. Miscellaneous abnormalities with associated renal tubular reabsorption defects	Oculo-cerebro-renal syndrome with hypophosphatæmic vitamin D-refractory rickets	Organic-aciduria, decreased renal ammonia production, hydrophthalmos and mental retardation.	0
	Other rare conditions		
B. Defective handling of other ions by the renal tubules resulting in calcium depletion			
i. Defective conservation of fixed base	Rickets due to renal tubular acidosis	Infantile renal acidosis, Lightwood's syndrome, hyperchloræmic renal acidosis (with nephrocalcinosis), Albright's syndrome (adult).	0
ii. Defective calcium reabsorption		Rickets due to idiopathic hypercalcuria.	0
IV *Miscellaneous*			
i. Defective calcification of bone matrix associated with generalized depression of alkaline phosphatase activity	Hypophosphatasia	Osteodysmetamorphosis fœtalis, osteoblastic dysostosis, rickets with low alkaline phosphatase activity.	4

(osteoid)[2] and in the pre-osseous cartilage at the zone of provisional calcification. The radiological and histological characteristics of this lesion are, of course, well known. The difficulties that frequently arise in interpreting the lesions in a given patient stem from the fact that the typical skeletal changes of rickets can be produced by several metabolically unrelated disturbances.

CLASSIFICATION OF RICKETS

In the past there was much disagreement concerning the fundamental disturbances giving rise to the various types of rickets, and much confusion regarding nomenclature. Although many of these problems cannot yet be resolved, the authors have undertaken to present a classification based upon current knowledge concerning the ætiology of the numerous known types of rickets (Table 18). The classification is not intended to encompass the various forms of osteomalacia that occur in adults.

Present evidence indicates that there are three main causes of rickets: (1) vitamin D deficiency, (2) chronic renal insufficiency, and (3) renal tubular insufficiency. For completeness, another category, (4) miscellaneous, has been added. To date, the latter includes only one condition—hypophosphatasia. The rachitic lesions attributable to the latter three categories do not respond to normal amounts of vitamin D.

By the use of standard diagnostic procedures, enumerated below, it is possible to fit any rachitic patient into the appropriate ætiological category and subdivision. As a result, a more rational definition of therapy and prognosis becomes possible.

NOMENCLATURE

In naming the various types of rickets, the authors have attempted to select for each a designation that is definitive. The large number of specific entities makes the task a difficult one and the terminology somewhat cumbersome. Proper names have been eliminated entirely, because their use caused much confusion in the past.

In particular, we concur with Professor Fanconi in eliminating "Fanconi syndrome,"[17] a designation that has been used indiscriminately to describe two entities now known to differ clinically, genetically and prognostically.

Although once a term of wider implication, "vitamin D-resistant rickets" has been used more recently to designate the specific syndrome defined under type III, A, i. We consider, as do others, that the alternative term "refractory" better expresses the present concepts of path-

ogenesis. We have chosen "hypophosphatæmic vitamin D-refractory rickets" as the explicit designation of the general group of rachitic lesions resulting from relatively intractable defects in the reabsorption of phosphate by the renal tubules (types III, A, i-vi).

GENERAL MEDICAL AND SURGICAL PROBLEMS IN WHICH THE DIAGNOSIS OF RICKETS SHOULD BE CONSIDERED

There is usually little difficulty in establishing the diagnosis of rickets, provided the condition is considered. However, the presenting manifestations of rickets may simulate a number of medical, surgical or neurological conditions.

The diagnosis of rickets should be considered in infants presenting with convulsions, tetany, general irritability, muscular weakness and delayed physical development. Because of the severe metabolic disturbances that accompany certain of the less common types (notably types III, A, iii, iv, vi), the diagnosis should be considered in infants and young children who fail to thrive.

In toddlers, rickets, especially types II, III and IV, should be considered in the differential diagnosis of such non-rachitic conditions as "physiological" bowing of the legs, tibial and femoral torsion, and osteochondritis tibiæ deformans (Blount's disease). In older children, dwarfism may be a major feature,[36] and the condition must be differentiated from achondroplasia.

PROCEDURE FOR CLASSIFYING AN ESTABLISHED CASE OF RICKETS

With rare exceptions, the diagnosis of rickets is readily established by (1) the typical radiographic appearance of the growing ends of the long bones, and (2) the demonstration of increased serum alkaline phosphatase activity. On very rare occasions histological studies of a costo-chondral biopsy may be required to prove the diagnosis of rickets.

On the other hand, the final categorization of an established case usually requires a number of diagnostic procedures, since no single symptom, physical sign, biochemical determination, radiographic appearance or histological characteristic can provide a reliable differentiation. The diversity of the possible manifestations of rickets places an equal obligation on physician and surgeon to understand the general principles of classification.

From both the therapeutic and prognostic standpoints, it is of prime importance to decide at the outset whether a given lesion is the result of vitamin D deficiency (type I) or whether it must be classified as one of the types of rickets that fail to respond to normal amounts of vitamin D (types II, III and IV). Usually the age of the

TABLE 19. *Usual Biochemical Findings in the Various Types of Rickets*

TYPE	TYPE OF RICKETS	BLOOD CHEMISTRY					URINE FINDINGS			TISSUE CYSTINE
		Calcium	Phosphorus	Alk. phosphatase	Urea	Acidosis	Glucose	Protein	Abnormal aminoacids	
I	Vitamin D deficiency rickets	N or ↓	↓	↑	N	0	0	0	+	0
II	Osteodystrophy due to chronic renal insufficiency (Pannephritic osteodystrophy)	↓ or N	↑	↑	↑	+	0	+	0	0
III	Rickets due to renal tubular insufficiency:									
A.										
i.	Hypophosphatæmic vitamin D-refractory rickets of the simple type	N	↓	↑	N	0	0 (rarely +)	0	0	0
ii.	Hypophosphatæmic vitamin D-refractory rickets with aminoaciduria	N or ↓	↓	↑	N	0	+	0 or +	++	0
iii.	Hypophosphatæmic vitamin D-refractory rickets with aminoaciduria and acidosis	N or ↓	↓	↑	N or ↑	+	+	+	++	0
iv.	Cystine storage disease with vitamin D-refractory rickets	N or ↓	↓ or ↑	↑	N or ↑	+	+	+	++	+
v.	Hypophosphatæmic vitamin D-refractory rickets with hyperglycinuria	N	↓	↑	N	+	0	0	+ (Glycine only)	0
vi.	Oculo-cerebro-renal syndrome with hypophosphatæmic vitamin D-refractory rickets	N	↓	↑	N	+	0 or +	+	++	0
B.										
i.	Rickets due to renal tubular acidosis	N	↓	↑	N	+	0	+	0	0
IV	Miscellaneous Hypophosphatasia	N or ↑	N	↓	N or ↑	0	0	0	+ (Phosphoryl-ethanolamine only)	0

0 = absent. + = present. N = normal.

patient, history, physical examination and the biochemical and radiological findings serve to answer the question. Occasionally in an infant with a questionable feeding history it may be impossible to differentiate between the "classical" and the "refractory" types. In this situation it is necessary to evaluate the response to a one-month therapeutic trial of vitamin D, administered as a daily dose of 3000 I.U., preferably in a water-miscible form.

Having eliminated vitamin D deficiency as the cause of a given rachitic lesion, it is important to ascertain next whether the rickets is attributable primarily to dysfunction of the glomerulus or the tubule. In most cases a clear-cut distinction can readily be made by a determination of the blood urea and serum inorganic phosphorus concentrations. Elevations of both indicate the presence of extensive glomerular insufficiency; a normal urea level and hypophosphatæmia indicate that the disturbance in renal function is localized to the tubules. However, secondary glomerular insufficiency may eventually develop in certain types of rickets in which tubular dysfunction is the primary lesion (types III, A, iii, iv, B, i); under these circumstances additional tests are required to complete the differentiation.

As The Hospital for Sick Children, Toronto, it is customary to carry out the following procedures on most rachitic patients at the time of the initial examination. Although additional procedures are occasionally required, those enumerated below usually sufficed to define the type of rickets with considerable precision. (1) History, including dietary and genetical aspects; (2) physical examination, including height and weight; (3) ophthalmoscopic examination of the cornea for presence of cystine crystals (see below); (4) routine urinalysis and urinary amino acid chromatography; (5) blood chemistry—total serum calcium, inorganic phosphorus and alkaline phosphatase; blood urea; serum electrolytes, base-combined bicarbonate and blood pH; (6) radiography—antero-posterior views of wrists and knees. Exposure settings are recorded for future reference. (7) Clinical photograph for future comparison.

The usual biochemical findings for the various types of rickets are indicated in Table 19.

INCIDENCE OF THE VARIOUS TYPES OF RICKETS

It is impossible to state with accuracy the incidence of the various types of rickets in the general population, but perhaps some idea of the relative incidence of the various syndromes may be had by noting the admissions to The Hospital for Sick Children during the 10-year period 1946-55 (Table 17).

Vitamin D deficiency rickets is still the most common type of

rickets in the predominantly urban population served by this hospital; of the lesions that persist despite the intake of normal amounts of vitamin D, the simple type of hypophosphatæmic vitamin D-refractory rickets is the most prevalent. Perhaps contrary to expectation, pannephritic osteodystrophy is relatively uncommon in children.

PATHOGENESIS OF RICKETS: PHYSIOLOGICAL CONSIDERATIONS

The normal deposition of calcium in growing bone and pre-osseous cartilage is dependent on (1) the integrity of intrinsic mechanisms within the proliferating matrix that control mineral deposition, and (2) the maintenance of physiological concentrations of calcium and inorganic phosphate in the serum. A disturbance of either or both these factors may result in rickets.

The maintenance of normal serum concentrations of calcium and phosphorus depends upon a delicate balance between the absorption of each element from the intestine, their excretion by the kidneys and intestine, and their rates of movement into or out of bone. Many factors, including vitamin D and parathormone, are necessary for the maintenance of physiological concentrations of calcium and phosphorus in the serum.

Space does not permit a comprehensive review of the modern and changing concepts of the rôle of vitamin D in calcium and phosphorus homeostasis and of its action upon the intrinsic mechanisms governing calcification in organic matrix. It has long been accepted that vitamin D increases the intestinal absorption of calcium and phosphorus. Recently it has been demonstrated also that diminished tubular reabsorption of phosphate[24] and of amino acids[26] occurs in the vitamin D-deficient infant, and that correction of both these defects is brought about by administration of vitamin D. These findings emphasize the important inter-relation of vitamin D, renal tubule function, and the rachitic state. Like parathormone, vitamin D (at least in large amounts) mobilizes calcium from bone.[23] However, by using a technique similar to that described by Fraser *et al.*,[21] it has been shown that vitamin D is not essential for calcium accretion in the vitamin D-deficient human being.[20] Whether it plays any rôle in this process is still open to debate.[5]

As yet it is impossible to assess the relative importance of the various physiological actions of vitamin D. Each of the foregoing considerations must be carefully evaluated in attempting to define the pathogenesis of the various types of rickets. The lack of fundamental knowledge concerning many of the mechanisms offers a wide scope for clinical investigation in this field.

CLINICAL ASPECTS OF THE VARIOUS TYPES OF RICKETS

The various types of rickets are described briefly in the following sections, and the therapeutic measures are outlined. For further details, the reader is referred to the medical literature.

Type I. Vitamin D Deficiency Rickets

The clinical features and the therapy of vitamin D deficiency rickets are well known. Healing of the lesion is brought about readily by the daily administration of 2000 to 3000 I.U. of vitamin D. Special precautions should be taken to prevent hypocalcæmia during the early phases of therapy. For infants the recommended prophylactic dose of vitamin D is 400 to 800 I.U.

Recent studies in Great Britain[30, 33] and the United States[9] have produced evidence that vitamin D hypersensitivity plays a rôle in the ætiology of idiopathic hypercalcæmia of infants. The present authors suspect that the fortification of evaporated milk with vitamin D has had a desirable effect upon the incidence of rickets in North America, but they advise against the use of prophylactic doses in excess of 1000 I.U. and deprecate the unwarranted addition of vitamin D to other commercially prepared foods.

Type II. Osteodystrophy Due to Chronic Renal Insufficiency (Pannephritic Osteodystrophy)

Pathogenesis. Although it has long been recognized that chronic renal insufficiency can result in skeletal lesions, the mechanisms by which these lesions are produced remain uncertain. Until recently it was held that diminished glomerular filtration of phosphate resulted in hyperphosphatæmia, which in turn resulted in secondary hyperparathyroidism of varying degree. Concomitant tubular damage has been thought to produce a failure of base economy which resulted in depletion of skeletal calcium and systemic acidosis.[42] However, the concepts of renal physiology are currently undergoing radical changes, and many of the ideas expressed above may require revision. At present it is probably safe to state that, in chronic renal insufficiency, the bones come under the influence of (1) a high concentration of parathormone, and (2) acidosis. In addition, recent evidence suggests the possible existence of (3) an unidentified factor that interferes with the intrinsic mechanisms of bone calcification.[47]

These various deleterious influences produce a skeletal lesion in which are combined, in varying degrees, the characteristic changes of both rickets and hyperparathyroidism.[18] We have named this lesion "osteodystrophy due to chronic renal insufficiency," and we suggest

the term "pannephritic osteodystrophy" as a more convenient, but, in a strict sense, less accurate substitute. The term "renal rickets" is misleading on two counts, and should be abandoned. "Renal" fails to draw a distinction between pannephritic and tubular ætiology, and "rickets" only partially describes the osseous lesion.

CLINICAL FEATURES. Theoretically, any abnormality that results in chronic renal insufficiency can cause pannephritic osteodystrophy. However, for some reason the latter condition is rarely seen in

Fig. 25. Osteodystrophy due to chronic renal insufficiency. Male: aged 14 years.

children, possibly because skeletal lesions develop slowly, and may not have become evident before terminal renal failure supervenes.

Symptoms and signs of chronic renal insufficiency (polyuria, hyposthenuria, albuminuria and nitrogen retention) antedate the onset of skeletal symptoms, usually by at least two years. Medical advice may be sought because of growth failure, bone pain, mild skeletal deformity (nearly always genu valgum) or hypocalcæmic convulsions.

The blood urea level is elevated, and the serum phosphorus and alkaline phosphatase concentrations are increased. The serum calcium concentration may be decreased or normal, acidosis is usually present, and aminoaciduria is absent (Table 18). The radiographic changes (Fig. 25) are those of (1) rickets (increased thickness of the epiphysial plate and fraying of the metaphysis in the region of the

zone of provisional calcification); (2) hyperparathyroidism (irregular disintegration of the sub-epiphysial metaphysis ("cotton wool appearance"), coarse irregular trabeculation, erosion or loss of definition of bone cortex in the long bones and metacarpals, and "tufting" of the terminal phalanges; and (3) generalized osteoporosis. The three lesions co-exist with varying degrees of prominence.

TREATMENT. Treatment consists in (1) appropriate medical and surgical management of the renal condition, and (2) measures directed toward improving the bone lesions.

Restriction of proteins to approximately 1 gm. per kilogram a day restricts phosphorus intake and thus tends to reduce the hyperparathyroidism. Phosphorus absorption is further decreased and calcium intake enhanced by giving calcium lactate (0.1 to 0.2 gm. per kilogram a day). Great caution should be exercised in controlling acidosis by the administration of alkalinizing potassium and sodium salts, since they may result in hyperkalæmia or tetany.

Promising results are currently being obtained by the cautious administration of increased amounts of vitamin D in pannephritic osteodystrophy.[14] During the early stages of therapy the patient should be observed carefully for evidence of increasing nitrogen retention, and the dose of vitamin D should be reduced considerably as soon as healing appears to be complete. In the present state of knowledge no conclusions can be reached concerning the effect of this new form of treatment upon the ultimate course of the underlying renal insufficiency.

Associated orthopædic problems should be treated conservatively; fatal uræmia may result from surgical intervention and prolonged immobilization.

Type III. Rickets Due to Tubular Insufficiency: General Remarks

It was recognized many years ago that certain cases of rickets failed to respond to usual therapeutic doses of vitamin D (2000 to 5000 I.U.). Some patients were shown to have chronic renal insufficiency (type II, pannephritic osteodystrophy, above). The remainder (type III) characteristically had no signs of glomerular failure, and many, except for their rachitic disabilities, were in excellent health. From a clinical standpoint the various syndromes included under type III presented a confusing picture which, until the adoption of modern biochemical techniques, defied logical explanation. However, during the past decade it has become increasingly evident that derangement in function of the renal tubule is present in all the syndromes included under types III, A and B.

Dysfunction of the renal tubule can result in rickets by two

mechanisms. In rare instances, disturbances in renal tubular function can result in sufficient urinary losses of calcium to produce rickets (type III, B). In practice, however, it has been demonstrated that almost always the tubular dysfunction is manifested by an increased renal clearance of phosphate (type III, A).

The exact nature of the vitamin D refractoriness in the latter group of rachitic patients is not yet completely understood. It has been demonstrated that intestinal absorption of vitamin D takes place readily.[1, 4] The intrinsic mechanisms of mineral deposition apparently are unimpaired.[5, 21] Although, characteristically, the urinary excretion of calcium is less than normal,[7, 40, 44] the latter finding has a variety of possible explanations. It does not rule out the now widely held contention that excessive renal phosphate clearance is the most important[7, 13, 17, 37] and possibly the only primary defect in rickets of this type. Large doses of vitamin D have been shown to reduce the excessive phosphate clearance in these patients.[13, 37] The demonstration of anatomical and histological lesions in the proximal convoluted tubules of some cases offers presumptive evidence that excessive phosphate clearance is attributable to inadequate reabsorption of this ion by the tubule.[11]

Several subdivisions of type III, A, are necessary. In the most common entity, hypophosphatæmic vitamin D-refractory rickets of the simple type, decreased tubular reabsorption of phosphate is the only demonstrable renal disturbance. However, largely as a result of the pioneer studies of Dent,[13] it is now evident that any combination of the many known functions of the renal tubule may be deranged. In Table 18 we presented an ætiological classification of the more important entities caused by this "spectrum" of renal tubule defects. We did so with the realization that additional syndromes have been reported, and that others will undoubtedly be discovered in the future, and also with the realization that new concepts of tubule physiology may necessitate revision of the classification.

Type III, A, i. Hypophosphatæmic Vitamin D-Refractory Rickets of the Simple Type[30]

Pathogenesis. As mentioned previously, increased clearance of phosphate is usually the only demonstrable renal defect in this syndrome. A familial incidence has been observed in many instances (Fig. 26), and recent studies suggest either sex-linked dominant[46] or autosomal dominant inheritance. Sporadic cases occur. Both sexes are involved.

Clinical Features. In this condition the only apparent biochemical abnormality is hypophosphatæmia. All clinical signs are referable to the

skeleton; the patient is otherwise in excellent health and has a normal life expectancy.

Skeletal deformities usually become evident at the commencement of weight bearing. Genu varum with femoral and tibial torsion is the most common deformity, but others may occur. Moderate dwarfing is usually present when the patient is first seen. The costo-chondral junctions and the large joints are prominent, the carrying angle of the elbow is usually lost, and frontal prominence may be present. Un-

Fig. 26. Hypophosphatæmic vitamin D-refractory rickets of the simple type. Three brothers and a female first cousin.

fortunately, in the past, considerable time usually elapsed before the refractoriness of the condition was recognized by the practitioner (two years, on the average, in our series). During a period of this order, deformities and dwarfing gradually became much more marked.

The total serum calcium concentration is normal, and tetany does not occur. The serum inorganic phosphorus concentration is low, and alkaline phosphatase activity is increased. The blood urea level and the urinary amino acid excretion are normal. Renal glycosuria is present in rare instances (Table 18).

Radiographs of the bones show the typical changes of rickets. However, because the metabolic disturbance is relatively mild, but of long duration, it is often possible to make a provisional radiological differentiation from vitamin D deficiency rickets. The thickness of the epiphysial plate is moderately increased, fraying of the metaphysis is

visible (but often not striking), and coarseness of the trabecular pattern is prominent.

TREATMENT. In 1937 Albright, Butler and Bloomberg[1] reported the satisfactory response of a patient to very large doses of vitamin D. Until recently this has been the only form of therapy available. At first, therapeutic results seemed excellent, but it is now becoming increasingly evident both here and elsewhere that treatment using massive doses of vitamin D is not entirely satisfactory because, in most cases, the optimal therapeutic dose lies within the general range of the amount that produces vitamin D intoxication.

In order to minimize the risk of cumulative vitamin D overdosage, the authors have adopted a conservative procedure for establishing the optimal subtoxic dose of vitamin D. Patients receiving vitamin D are examined at monthly intervals until the maintenance dose is established, and thereafter every two or three months until the end of puberty. At each examination the parent is interviewed and the following determinations are made: height and weight; serum calcium, phosphorus, alkaline phosphatase and urea concentrations; urinalysis (including Sulkowitch test and specific gravity). Radiographs and clinical photographs are taken at intervals of about six to 18 months as required.

A normal balanced diet is prescribed. Synthetic vitamin D_2 (calciferol) is administered orally, starting with a daily intake of 40,000 to 50,000 I.U. (1.0 to 1.25 mg.). Initially, the daily dose is increased by 25,000 I.U. at intervals of not less than one month. Larger increments are added when the dose exceeds 150,000 I.U. a day.

In this manner the vitamin D dosage is increased until either (1) complete healing is attained or (2) mild intoxication is produced. At the earliest evidence of intoxication, vitamin D is discontinued for two weeks. If, after this interval, all signs of toxicity have disappeared, vitamin D therapy is resumed, giving a daily dosage 25,000 I.U. less than previously. From time to time minor adjustments in dosage are required during the growth period, since the objective of therapy is to maintain a maximal degree of healing without vitamin D intoxication.

Although it is conceivable that considerable reduction in dosage may be practicable after puberty, patients have been reported who suffered from active disease in childhood, became symptom-free in their twenties, but had severe osteomalacia in their later years.[15] Therefore, in patients past puberty, it would seem advisable to administer sufficient vitamin D to maintain a normal serum phosphatase activity and a serum phosphorus concentration above 2.5 mg. per 100 ml.

Although equal amounts of dihydrotachysterol (A.T.10) have been shown to be equally effective in the treatment of hypophosphatæmic

vitamin D-refractory rickets,[24, 39] the present authors doubt that this costly drug offers any advantages.

It can be surmised that the ideal therapeutic regimen would result in (1) establishment of physiological serum calcium, phosphorus and alkaline phosphatase concentrations; (2) normalization of the radiographs of the skeleton; and (3) establishment of a normal growth rate. The efficacy of any treatment must be assessed on the basis of these criteria of complete healing.

The criteria of early vitamin D intoxication are (1) anorexia, irritability, lassitude; (2) weight loss or cessation of normal weight gain; (3) polydipsia, polyuria (especially nocturia); (4) hypercalcæmia (above 11.5 mg. per 100 ml.); and (5) elevation in the blood urea level. These toxic manifestations are reversible if vitamin D is withheld promptly and copious amounts of fluids administered. However, if hypercalcæmia is allowed to continue, generalized vascular calcification and chronic renal insufficiency supervene.

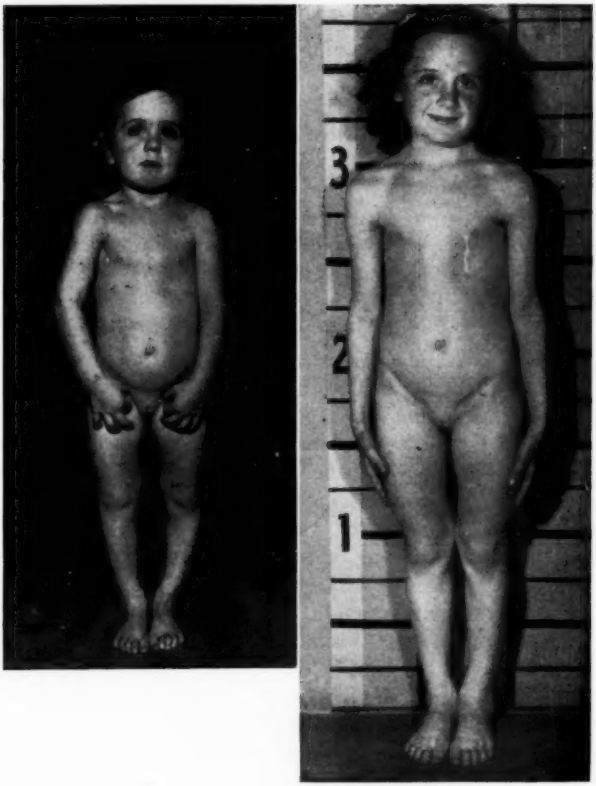
It has been our experience that, with careful instruction, the parents can readily recognize the early signs of vitamin D intoxication. We no longer instruct the parents to use the Sulkowitch reagent. Gradual attainment of the optimal therapeutic dosage of vitamin D by the method described ensures rapid recovery from toxicity after vitamin D has been withheld. To date none of our patients has had recognizable sequelæ to the minor degrees of intoxication that have occasionally occurred.

In order to obtain warning of impending intoxication, Stearns and her associates have recently evolved a procedure that deserves further trial.[40] Since the urinary calcium output of children with untreated hypophosphatæmic vitamin D-refractory rickets has been shown to be less than that of normal children, they define the optimal therapeutic dose of vitamin D as that amount required to establish a calcium output that falls within the somewhat wide normal range established by Knapp.[27] To determine the proper dose, they merely require estimates of the patient's body weight and calcium intake, and a knowledge of the 24-hour urinary calcium output.

Saville *et al.* have combined oral phosphate supplements with dihydrotachysterol or calciferol in the treatment of this condition.[39] They state that these measures reduce the toxicity of vitamin D and maintain the serum inorganic phosphorus concentration above 4 mg. per 100 ml.

Results of Treatment. It is generally agreed that considerable benefit is to be expected from the use of large doses of vitamin D in the treatment of most cases of hypophosphatæmic vitamin D-refractory rickets of the simple type. However, in one of our patients vitamin D

was of no value, because intoxication resulted from a dose that produced no clinical, biochemical or radiological evidence of healing. Our experience with 11 additional cases of this syndrome has shown that progression of the deformities was arrested by vitamin D therapy



A B

Fig. 27. Hypophosphatæmic vitamin D-refractory rickets of the simple type. *A*, Aged 4 years. No therapy. *B*, Aged 8 years. Note improvement while receiving optimal subtoxic doses of vitamin D.

in all but two patients; in most, steady orthopædic improvement occurred (Fig. 27).

On the other hand, although vitamin D therapy must exert some beneficial effect on growth, its efficacy in promoting good skeletal growth was disappointing. If one compares the growth of our patients with that of the normal population (Fig. 28), the following defects

become evident. None of the patients attained average height, although vitamin D intake had been gradually raised above, and maintained at, the maximal limit of tolerance (50,000 to 450,000 I.U.) in all but one case. The heights of one quarter of the patients reached the 3 percentile of normal, but the statures of the remainder fell below this range, some very much below. A corresponding lack of adequate response to optimal doses of vitamin D was reflected in the serum

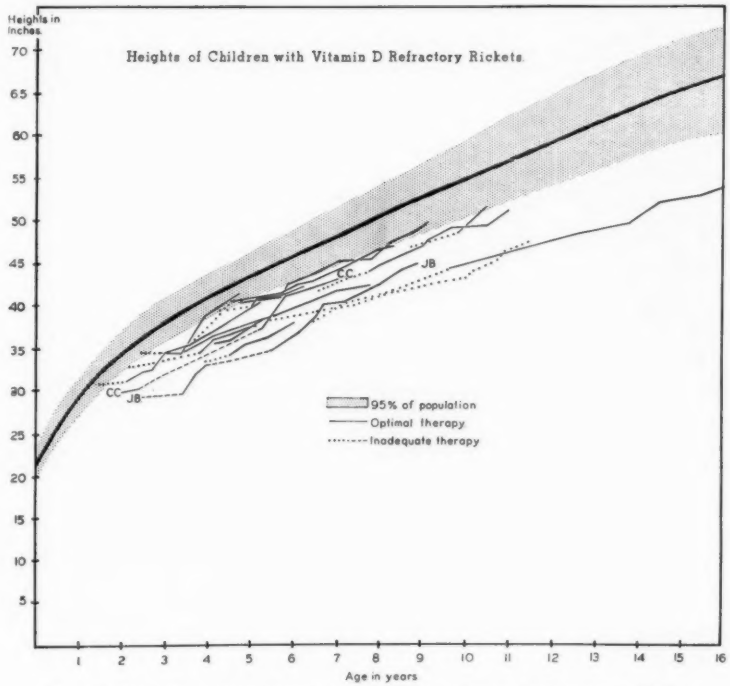


Fig. 28. Growth pattern of 14 children with vitamin D-refractory rickets.

phosphorus and alkaline phosphatase values of treated patients (Table 20), and in the persistence of coarse trabecular markings or minor epiphysial lesions in the radiographs of more than half the cases.

It has been stated, largely on the basis of radiographic evidence, that the establishment of a normal serum phosphorus concentration is not a prerequisite for healing in hypophosphatæmic vitamin D-refractory rickets.[22] On the contrary, we have observed, in studying the responses of the individual patients to therapy, that the radiographic picture provided an unreliable estimate of the patient's progress, but that the

TABLE 20. *Effect of Vitamin D Therapy on the Serum Chemistry of 15 Cases of Hypophosphatæmic Vitamin D-Refractory Rickets*

DIAGNOSIS	THERAPEUTIC STATUS	MEAN TOTAL CALCIUM (MG./100 ML.)	MEAN INORGANIC PHOSPHORUS (MG./100 ML.)	MEAN ALKALINE PHOSPHATASE (KA UNITS)
Normal Range		9.5–11.0	4.3–6.0	8–16
Type IIIA,i (12 cases)	Before therapy	10.4	2.7	53
	During optimal vitamin D therapy	10.3	3.3	27
	During vitamin D intoxication (10 cases)	13.2	3.8	16
Type IIIA,ii (3 cases)	Before therapy	9.2	2.3	111
	During vitamin D therapy	10.6	4.8	19.9

biochemical data correlated well with the patient's growth. Experiments now in progress at this hospital suggest that the serum phosphorus concentration may prove to be the most important single factor in determining the status of the rachitic lesion. It is hoped that these experiments may eventually provide a basis for a safer and more effective management of this disease.

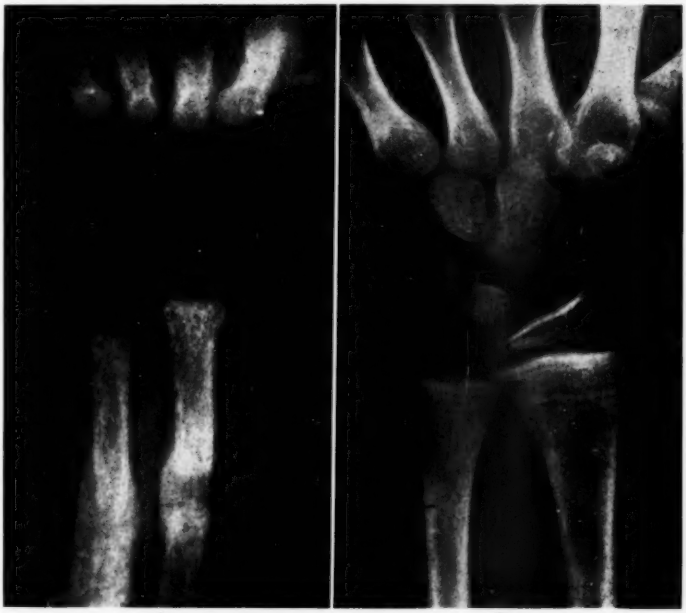
Type III, A, ii. Hypophosphatæmic Vitamin D-Refractory Rickets with Aminoaciduria

The clinical features of this rare syndrome are similar to those of Type III, A, i. However, in our experience the onset tends to be earlier, the rachitic lesion is very much more severe, and muscular weakness is prominent. Radiographs show evidence of florid rickets and often pathological fractures (Fig. 29, A). In our experience, deformities have not been severe, probably because the child is usually unable to bear weight.

Biochemical findings are indistinguishable from those of severe vitamin D deficiency rickets except that generalized aminoaciduria is more marked. Plasma amino acid concentrations are normal. Hypocalcæmia may be a feature. However, the condition is readily distinguished from vitamin D deficiency rickets by demonstrating a lack of response to normal therapeutic doses of vitamin D. The entity under discussion and the two that follow (types III, A, iii, iv) have frequently been referred to as the "Fanconi syndrome."

We consider that the differentiation of this disease from the simple type of hypophosphatæmic vitamin D-refractory rickets is of great therapeutic and prognostic importance. Our experience with three

cases indicates that, when large doses of vitamin D_2 (100,000 I.U. in each case) were administered, rapid and apparently complete radiographic healing of the epiphysial lesions took place without vitamin D intoxication (Fig. 29, *B*). The serum calcium, phosphorus and alkaline phosphatase determinations became normal in two cases treated for a four-year period (Table 19), pathological aminoaciduria disappeared completely, and deformities tended to regress favourably on adequate vitamin D therapy. It is our impression that there was a significant



A B

Fig. 29. Hypophosphatæmic vitamin D-refractory rickets with aminoaciduria. Wrist (*A*) at age 2 years. No therapy. (*B*) At age 8 years. Optimal dosage of vitamin D_2.

improvement in the growth rate during vitamin D therapy (Fig. 28, cases C.C. and J.B.).

From our limited experience we suggest that patients of this type probably have an excellent prognosis if the diagnosis is made at an early stage. In our third case, diagnosed at the age of eight years, some six years after the onset of symptoms, cirrhosis had already developed with a secondary malignant hepatoma. Similar hepatic changes have been reported previously in children and adults suffering from vitamin D-refractory rickets with aminoaciduria,[25, 41] but whether chronic amino acid losses are ætiological remains unconfirmed.

Type III, A, iii. Hypophosphatæmic Vitamin D-Refractory Rickets with Aminoaciduria and Acidosis[15]

In a certain group of patients tubular dysfunction may also affect acid-base regulation.

In infants the clinical features are similar to those of cystine storage disease (type III, A, iv), and there has been some argument whether these patients may, in fact, represent undiagnosed examples of the latter condition. We favour the opinion that the two entities are entirely distinct. Treatment wih alkalis and large doses of vitamin D probably offers a better prognosis than exists for cystine storage disease, but the metabolic derangements are complex, and prognosis should be guarded.

Cases with similar biochemical disturbances may present with manifestations of varying severity, and at any age from infancy to middle age. In some, diminished phosphatase activity has been demonstrated in the proximal tubules. Large doses of vitamin D decrease the abnormal renal clearance of phosphate, glucose and amino acids, and combined therapy using vitamin D and alkalis has yielded favourable results. Cirrhosis has been reported in a few long-standing cases.[41]

Type III, A, iv. Cystine Storage Disease with Rickets[8]

Pathogenesis. Although most of the early manifestations of cystine storage disease are directly attributable to renal tubular insufficiency, there exists a generalized defect in the metabolism of cystine whereby large amounts of this amino acid are deposited in various tissues of the body. From clinical observations it is probable, though not proved, that the derangement in cystine metabolism is the primary lesion and that the renal lesion is secondary. The disease appears to be determined by a heterozygous recessive gene,[6] but the biochemical explanation for the cystine deposition is unknown. In association with the renal dysfunction, a specific anatomical lesion of the proximal tubules has been noted.[11]

Clinical Aspects. The clinical manifestations of cystine storage disease apparently depend upon the severity of the renal lesions. In the acute form, failure to thrive, polyuria, renal glycosuria, dehydration, acidosis, hypokalæmia and emaciation are common features and usually appear within the first year of life. Rickets may be present or may not develop until later. The usual biochemical findings are shown in Table 18. The chronic form usually presents in the second or third year of life. The typical manifestations are dwarfism, rachitic deformities and often photophobia.

The presence of insoluble cystine crystals in various tissues is the pathognomonic feature that differentiates the disease from all other

forms of rickets. Birefringent crystals are visible in unstained bone marrow aspirate examined under Nicol prisms, and minute, shimmering, white particles can be seen in the cornea by slit-lamp examination.

A much more convenient, and in our experience a surprisingly reliable method of demonstrating the crystals in the cornea is by use of the +40 dioptre lens of the standard ophthalmoscope. By using this procedure the provisional diagnosis of cystine storage disease was correctly made in each of our six confirmed cases, and, to date, no falsely positive diagnoses have been made. This simple technique should be used in the routine physical examination of all patients with "resistant" rickets.

TREATMENT AND PROGNOSIS. Treatment consists in administering oral alkalis to correct the acidosis, potassium to correct or prevent hypokalæmia,* and large doses of vitamin D to improve the rachitic lesions. The risk of producing dangerous hypokalæmia during the performance of the glucose tolerance test should be borne in mind. Intensive therapy does much to improve the general condition of the patient, and usually produces healing of the rachitic lesions. However, the therapeutic measures at present available have no apparent effect on the disordered metabolism of cystine. Except in rare instances,[12] glomerular involvement eventually occurs, and death results from uræmic or hypokalæmic crises, usually before the age of 10 years.

Type III, A, v. Hypophosphatæmic Vitamin D-Refractory Rickets with Hyperglycinuria[15]

This recently described rare syndrome has its onset in adolescence or early adult life, and is characterized by severe osteomalacia, severe muscle weakness, hypophosphatæmia, hypercalcuria, acidosis and excessive urinary excretion of glycine. Response to large doses of vitamin D has been moderately satisfactory.

Type III, A, vi. Miscellaneous Abnormalities with Associated Renal Tubular Reabsorption Defects

OCULO-CEREBRO-RENAL SYNDROME. In this rare condition are associated congenital glaucoma, mental deficiency, acidosis, aminoaciduria and usually hypophosphatæmic vitamin D-refractory rickets. For further details, the reader is referred to the original report.[29]

* The authors have given the following mixture[28] with satisfactory results:

Sodium citrate	50 gm.	Dose: 15–50 ml. mixed with orange juice 4 or 5 times daily as required.
Potassium citrate	50 gm.	
Citric acid	60 gm.	
Water to	1000 ml.	

Other Conditions in Which Hypophosphatæmic Rickets or Osteomalacia Has Occasionally Been Reported. These include (*a*) hepato-lenticular degeneration,[43] (*b*) multiple myelomatosis,[16] (*c*) neuro-fibromatosis,[38] (*d*) chronic lead poisoning.[10]

Type III, B. Defective Handling of Other Ions by the Renal Tubules Resulting in Calcium Depletion

Rickets Due to Renal Tubular Acidosis.[28] The various forms of renal tubular acidosis of infants and children are rare in North America, and the clinical features will not be described here. Protracted urinary losses of fixed base produce gradual depletion of calcium, but clinical rickets is rarely observed. Control of the acidosis is followed by healing of the rachitic lesions.

Idiopathic Hypercalcuria. Adults are occasionally encountered who excrete large quantities of calcium in the urine despite normal serum calcium and acid-base determinations. Although in adults osteomalacia has occasionally resulted,[2] rickets due to this cause has not been reported in childhood.

Type IV. Miscellaneous

Hypophosphatasia. Hypophosphatasia is a genetically determined metabolic disease characterized by three salient features: (1) abnormal mineralization of bone, (2) diminished alkaline phosphatase activity in serum and tissues, and (3) increased urinary excretion of phosphoryl-ethanolamine. Although the bone lesions have certain similarities with those of the other types of rickets, thus justifying the inclusion of this disease in the general classification of rickets, the biochemical findings are dissimilar. The osseous lesions are considered to be due to a disturbance in the intrinsic mechanisms concerned with the elaboration of organic bone matrix or its calcification, or both.[19]

THE ORTHOPÆDIC MANAGEMENT OF RACHITIC DEFORMITIES

The common orthopædic deformities associated with the various long-standing types of rickets include genu varum, genu valgum, femoral torsion, anterior angulation of the femora, coxa vara, intrapelvic protrusion of the acetabulum, kyphosis and scoliosis. The upper extremities, though usually shortened, are less frequently deformed because they do not support body weight.

Because deformities are prominent in many types of rickets, the surgeon is frequently the first specialist to be consulted. He must, therefore, be fully cognizant of the differential diagnosis of the various rachitic disorders and must work in close association with the physician

responsible for the medical management. If the surgeon fails to recognize an underlying rachitic lesion, the deformities will invariably recur after surgical correction. On the other hand, once the rickets has been brought under satisfactory medical control, the deformities tend to regress considerably. This improvement can often be enhanced by appropriate splinting of the lower limbs during the sleeping hours. By using the splints during the night, continuous influence is exerted upon epiphysial growth for a period of at least 12 hours daily. This procedure usually corrects the less severe deformities in approximately six months, and we consider it preferable to the use of heavy awkward and less efficient day-braces.

If, in spite of adequate medical therapy and conservative orthopædic measures, severe rachitic deformities persist, operative correction is indicated. In such a case it is imperative to discontinue intensive vitamin D therapy at least three weeks pre-operatively in order to avoid the risk of severe hypercalcæmia, which otherwise would occur on immobilizing the patient. Surgical intervention is contra-indicated if chronic renal insufficiency is present.

Osteotomy of a curved or "dome" type is the most satisfactory operative procedure and should be performed through the cancellous metaphysial region of the long bone, not only because the deformity can be more accurately corrected at this site, but also because union occurs more rapidly. The patient is made ambulatory as early as possible, at which time vitamin D therapy is resumed.

SUMMARY

Although vitamin D deficiency is no longer a serious pædiatric problem, a heterogeneous group of rachitic infants and children still exists, many of whom fail to respond to conventional doses of vitamin D. The application of modern clinical methods has resulted in the delineation of several distinct types of rickets, and much is now known about the pathogenesis of each. Since current therapeutic measures frequently can offer the patient a great deal of benefit, it is incumbent upon both physician and surgeon to understand the classification of rickets.

In this paper the authors have presented a scheme to aid in establishing the nature of a given rachitic lesion. They have summarized the characteristic clinical features of the various types of rickets and some of the present concepts of medical and orthopædic management.

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CONGENITAL OESOPHAGEAL STENOSIS

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In the past five years five cases thought to be examples of congenital œsophageal stenosis have been encountered in the Department of Radiology of The Montreal Children's Hospital. In view of the supposed rarity of the condition, and the confusion regarding it in the available medical literature, these cases will be presented. Criteria for making the diagnosis on radiological and clinical grounds, supported by pathological examination when resection becomes necessary, will be suggested.

CASE HISTORIES

CASE I. D.D., a male aged 3 years, vomited for the first 3 weeks of life, but then the vomiting stopped, and he had no further trouble until solid foods were added to the diet. From that time on there was always difficulty in ingesting any solid food. The mother stated that raisins or pieces of potato or 'junior food,' unless very fluid and strained, would be vomited. Ten days before admission the child had swallowed a plum pit. Since then he had vomited consistently almost everything swallowed.

The child was well developed and well nourished and in no acute distress. There were a few enlarged cervical lymph nodes bilaterally. Otherwise the physical examination was negative. X-ray examination of the œsophagus (Fig. 30, *A*) showed a constriction at approximately the junction of the middle and distal thirds. It appeared to be smooth. Immediately above it was a filling defect in the œsophagus, approximately the size of a plum pit. Proximal to the constriction the œsophagus showed moderate dilatation.

Two days after admission to hospital the child vomited the plum pit. Œsophagoscopy done the day after the plum pit was vomited, showed an œsophageal stricture. There was no significant inflammatory change at the level of the stricture. The œsophagoscope was passed through the stricture, and the œsophageal mucosa beyond it appeared to be normal. It did not resemble gastric mucosa. No biopsy was done. Four days after admission x-ray examination was repeated. A catheter was passed through the stricture and opaque medium gently injected both proximally and distally (Fig. 30, *B*). This showed the stricture to be composed of 2 membrane-like constrictions with what appeared to be normal œsophagus, or at least œsophagus showing less constriction, between them. Proximal to this, moderate dilatation was again shown. Distal to it the œsophagus appeared normal, with normal peristaltic activity. There was no evidence of gastro-œsophageal reflux in any position, including the Trendelenburg (head-down) position.

Œsophageal dilatations at monthly intervals were begun. They were done initially under direct vision and subsequently without direct vision, using mercury bougies. This was carried on for approximately one year, when a mercury no. 30 bougie could be passed without difficulty. Since then (approximately 10 months) this child has done well. He sometimes has difficulty when attempting to eat quickly, particularly hot dogs. There is no other difficulty with swallowing.

Case II. C.F., a female aged one year, began to have difficulty in swallowing around the age of 8 months when she was first given solid food. The difficulty in swallowing became more marked at the age of 10 months. Approximately 2 weeks before admission she became able to retain only fluids. On admission she was a well-nourished one-year-old child, in no distress. No physical findings were reported relevant to the history.

Plain films of the chest and abdomen showed two disk-like semi-opaque foreign bodies, about 1 cm. each, in the œsophagus, arrested at a point just below the tracheal

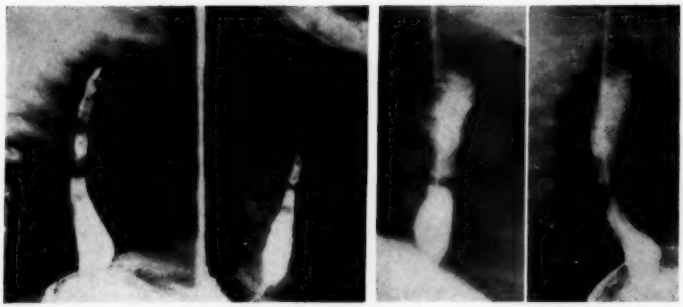
A B

Fig. 30. *A*, Œsophagus containing foreign body (plum pit) above stenosis. *B*, During injection of opaque medium (barium sulphate suspension) into distal œsophagus. "Double" stenosis clearly shown, with normal œsophagus distal to stenosis.

bifurcation. The œsophagus above this appeared to be dilated, as shown by anterior displacement and compression of the trachea. This œsophageal dilatation raised the suspicion of a stenosis, complicated by impaction of foreign bodies. Œsophagoscopy done the same day showed the 2 foreign bodies to be 2 toy rubber tires. In addition, pieces of straw, paper and cabbage were removed from the proximal œsophagus. At approximately 16.5 cm. from the upper teeth the œsophagoscope (no. 5) would go no farther because of narrowing of the lumen. The mucosa was mildly œdematous.

The day after admission, radiological examination of the œsophagus was done (Fig. 31, *A*). A constriction of the œsophagus approximately 2 cm. below the level of the tracheal bifurcation was demonstrated, but was not clearly defined. A catheter was then passed to and through the suspected area and barium fluid injected (Fig. 31, *B*). A well-defined, short, circular constriction was demonstrated at approximately the junction of the middle and distal thirds of the œsophagus. Distal to this constriction the œsophagus appeared normal, and in particular there was no evidence of hiatus hernia or gastro-œsophageal reflux.

Dilatation of the œsophagus was begun after removal of the foreign bodies, and is being continued. At the time of writing, 5 months after the initial admission, œsopha-



A B

Fig. 31. A, Œsophageal constriction demonstrated after removal of multiple foreign bodies. B, Opaque medium injected through catheter shows short, well-defined stenosis. Distal œsophagus normally distensible. No hiatus hernia or gastro-œsophageal reflux was demonstrated.

geal dilatations are being carried out at intervals of approximately one month. The child is able to swallow anything, except large pieces of meat, without difficulty.

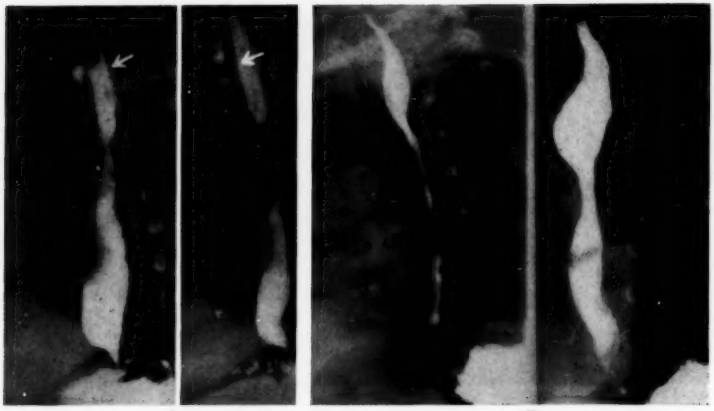
CASE III. C.B., a female aged 3 years, had a history of difficulty with feeding since birth. She would cough with each feeding and frequently turn blue. She always had difficulty eating any solid food and frequently vomited ingested solids. Until admission, at age 3, she had continued to have coughing and choking spells when drinking, particularly when drinking rapidly. Up to the time of admission she was drinking about 2 quarts of milk daily and eating some pablum, but no solid food. She was not coughing between meals. She was otherwise a healthy child who was active and did not tire easily. Other history was non-contributory.

She was a well-developed and well-nourished white child in no acute distress. She had a moist cough. X-ray examination immediately before admission to hospital showed (Fig. 32, A) a tracheo-œsophageal fistula, at approximately the level of the first dorsal vertebra (thoracic inlet). Extending downward for a distance of approximately 1.5 cm. from the level of the tracheal bifurcation was an œsophageal stenosis of moderate severity. This was shown with and without passage of a catheter, for injection of barium sulphate.

On œsophagoscopy an area of stenosis approximately 1 to 1.5 cm. in length was observed at a distance of 18 to 20 cm. from the upper teeth. The wall of the œsophagus appeared healthy with no scarring. Mercury bougies from no. 14 to 26 were passed, the 26 encountering slight resistance on insertion and more resistance on withdrawal. There was no bleeding. It was felt that the lumen at the level of the stenosis would be adequate for all food except for a large bolus of meat or other similar food.

Approximately 2 weeks after admission a thoracotomy was done, and the tracheo-œsophageal fistula was identified, divided and closed. The post-operative course was satisfactory, and the child was discharged 6 weeks after admission. During the first 5 months after discharge 2 œsophageal dilatations were done in the Out-Patients' Department. When last seen (November, 1957), approximately 6 months after admission, the child was doing well with no further coughing during meals. Large pieces of meat could not be swallowed. No other food gave any difficulty, and she was growing and developing normally.

CASE IV. M.O., a male aged 6 years on last admission, was first admitted to hospital at age 27 months with a history of regurgitating all solid food. The father had stated that the boy had been well, except for some eczema, up to the age of one year. At that



A B

Fig. 32. *A*, Tracheo- œsophageal fistula demonstrated at superior thoracic inlet, with œsophageal stenosis just below level of tracheal bifurcation. *B*, After fistula divided and closed. Œsophageal stenosis better shown with œsophagus distended than partially collapsed.

time the parents noticed that he would regurgitate all solid food given him. The father stated that the food appeared to go down for a short distance, and then he would cough and choke until it came back. He took fluid and strained baby food without difficulty. In early infancy he had been a slow feeder at the bottle, but had had no vomiting. Weight gain and nutrition had been normal.

X-ray examination at the age of 27 months (Fig. 33) showed a well-defined stenosis at approximately the junction of the middle and distal thirds. By injecting barium sulphate at and below the stenosis with a catheter, the constriction was shown to be

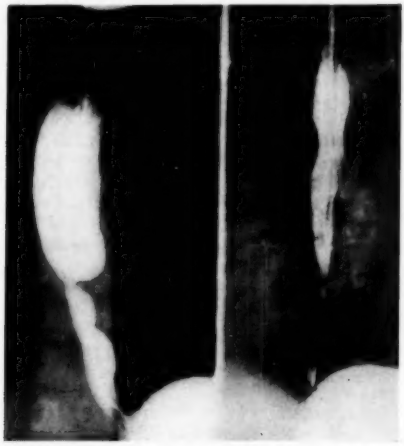


Fig. 33. A well-defined stenosis with 2 distinct constrictions demonstrated by catheter injection.

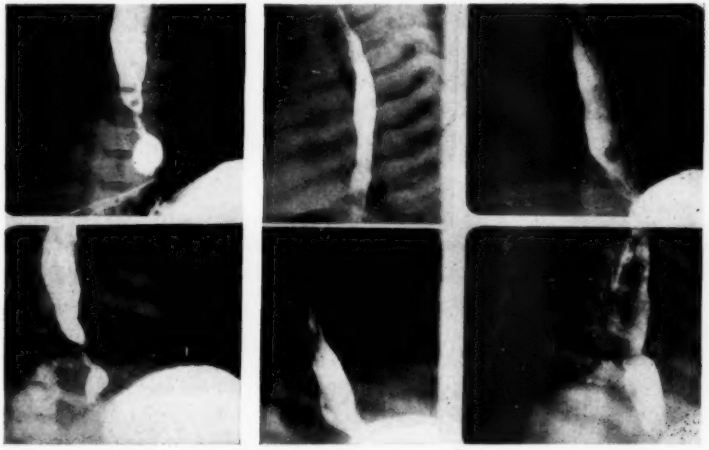
a double one with an intervening relatively normal segment, approximately 1 cm. in length, between 2 short and well-defined circumferential constrictions.

After this, œsophageal dilatation was carried out with only partial success. At age 6½ years thoracotomy was done. The œsophagus appeared normal, and in particular there was no evidence of œsophagitis, peri-œsophagitis or hiatus hernia. The stenosis could be located only by passing a catheter down the œsophagus to the point where it was arrested. A segment measuring about 2.25 cm. in length was resected and end-to-end anastomosis performed. A catheter could then be passed into the stomach with ease. At age 7 he was re-admitted for dilatation. A mild stricture had developed post-operatively, but it had never caused severe symptoms and was not difficult to dilate.

He was 7 years old when last seen and was having no difficulty in swallowing anything but large pieces of meat. X-ray examination revealed slight irregularity of the œsophageal wall at the site of the resection, but no definite stenosis.

Pathological examination of the resected specimen was reported (Pathologist, Dr. F. W. Wiglesworth) as follows: "Congenital stenosis of the junction of middle and lower thirds of the œsophagus, showing minimal to moderate scarring of the submucosa and muscularis with hypertrophy of the latter."

Case V. P.T., a female aged 7 months, was well until about 6 weeks of age, when the mother began to give solid food. At this time the child was unable to swallow the



A B

Fig. 34. A, A short well-defined stenosis in lower œsophagus, with normal œsophagus distal to it. B, After excision of stenosis. Site of anastomosis just identifiable.

food, and from then until admission at age 7 months the diet had consisted of milk and egg yolks. The child always appeared to be hungry. On physical examination the patient was small, but well developed and pale. Hæmoglobin was 8.9 gm. The remainder of the physical and laboratory examinations was negative.

X-ray examination showed (Fig. 34, A) a well-defined stricture, about 1 cm. in length in the lower œsophagus, about 2 cm. from the gastro-œsophageal junction. Distal to this the œsophagus appeared normal. There was no evidence of any hiatus hernia on the films. The fluoroscopic report, however, did not specify absence of gastro-œsophageal reflux.

Approximately 2 weeks after admission a thoracotomy was done. The œsophagus did not appear to be abnormal on inspection, but on palpation a thickened muscular wall could be palpated. Approximately 1.5 to 2 cm. of this thickened segment was

resected. A direct end-to-end anastomosis was done. The post-operative course was satisfactory. Six weeks after operation, examination of the œsophagus (Fig. 34, *B*) showed a slight constriction identifiable only with difficulty.

After discharge the child was not seen again, but inquiries through relatives up until the age of 20 months after operation revealed that there had been no further difficulty with swallowing. The child was growing and developing normally.

Pathological examination of the resected specimen was reported (Pathologist, Dr. F. W. Wiglesworth) as follows: "Congenital stenosis of the lower one-third of œsophagus showing moderate scarring of the sub-mucosa and muscularis with hypertrophy of the latter."

DISCUSSION

No clear concept of the incidence or importance of congenital œsophageal stenosis appears to have evolved in the medical literature. The reasons for this are as follows: (1) It is comparatively rare. We believe, however, that it is not as rare as formerly supposed. (2) The attention of physicians and surgeons has been directed toward the much commoner and more urgent congenital œsophageal atresia. This is particularly true since surgical therapy has radically altered the previously hopeless prognosis of œsophageal atresia. (3) The controversy centering around the gastro-œsophageal junction, the œsophageal diaphragmatic hiatus and reflux œsophagitis has caused confusion in the classification of œsophageal stenosis.

INCIDENCE

A true idea of the incidence of congenital œsophageal stenosis is not available from the published data. Astley[3] lists it as the least common of the anomalies involving the œsophagus and tracheobronchial tree and states that "most of the alleged examples described in the past were really strictures due to reflux œsophagitis." Gross,[13] on the other hand, lists 38 cases from his department, but notes that, "in the quarter (of the cases) which we have seen in the lower third of the esophagus, it is not always clear whether the narrowing was one which had existed since birth or whether it represented scarring and cicatricial contraction after peptic ulceration and esophagitis." He does not document the cases individually as to the radiological and endoscopic and pathological findings and, in particular, with reference to the distal œsophageal segment and the condition of the mucosa at the level of the stenosis.

Between these two extremes in concepts of incidence there are many statements noting only that the entity does occur; e.g., "congenital stenosis of the œsophagus, without fistula formation, can be found at any point along the œsophageal lumen, as either a web or a long segment of esophagus with only a threadlike lumen" (Nelson[23]).

In 1928 Beatty[4] reviewed all the cases listed as congenital œsophageal

stenosis and found 50 which appeared to him to be satisfactory, and to these he added 7. Some of these 57 cases would not now be accepted as congenital œsophageal stenosis, in view of the inadequate study of some cases and, in particular, incomplete appreciation of the possibility of gastro-œsophageal incompetence with or without hiatus hernia. However, some of them, particularly those with a thin, well-defined membrane, appeared to be clearly of congenital origin.

In 1929 Abel[1, 2] reported one case of an imperforate congenital web, just below the level of the tracheal bifurcation, which he ruptured by pressure with the œsophagoscope and thereby cured the patient.

In 1932 Findlay[11] reviewed 80 cases of œsophageal stenosis in children, and found only 23 adequately documented. Of these, nine had a narrowing of the lumen at various levels, four had membranous obstructions at or below the bifurcation, eight had localized fibrous or fibromuscular thickening at diverse levels, and two he classified as spasm.

Sporadic reports of congenital œsophageal stenosis have appeared since 1932,[12, 26, 33, 34] many poorly documented.[12, 15, 18, 19, 20, 22, 31]

REFLUX ŒSOPHAGITIS

A vast literature has accumulated on the subject of reflux œsophagitis and its causation and effects both in infancy and adult life. Without attempting to enter into, much less solve, this controversy, it may be fair to make the following suggestions about reflux œsophagitis:

1. Gastro-œsophageal reflux occurring occasionally in infancy is a normal phenomenon. Unless it occurs in severe degree and persistently, it should not be regarded as significant. This was recently shown by Silverman[30] in a study of normal infants.

2. Gastro-œsophageal reflux does occur to an abnormal degree in the presence of obstruction distal to the gastro-œsophageal junction (cardia) anywhere in the upper intestinal tract and particularly at the pylorus. When this lower obstruction is relieved (as in the Ramstedt operation for hypertrophic pyloric stenosis), the reflux characteristically disappears.

3. Gastro-œsophageal reflux occurring constantly and markedly from any cause can and does produce "peptic œsophagitis."[3, 29] This may be followed by fibrosis, ulceration and "cicatricial stenosis" of the œsophagus. Such stenosis is most likely to be at, or just above, the gastro-œsophageal junction.

4. Gastro-œsophageal reflux can be caused by inadequacy of the gastro-œsophageal sphincter mechanism, with or without diaphragmatic hiatus hernia. Regarding the importance of hiatus hernia itself, versus

simple gastro-œsophageal sphincter incompetence, in the causation of gastro-œsophageal reflux, there is still no general agreement.[29, 30]

5. Œsophageal stenosis secondary to peptic œsophagitis should, if possible, be distinguished from simple congenital œsophageal stenosis.

SECONDARY (CICATRICIAL) STENOSIS

This term should include all cases of œsophageal scarring, including that secondary to ingestion of corrosives (e.g., lye), but for purposes of this discussion will be restricted to those cases secondary to peptic œsophagitis. The following features would appear to allow distinction of this entity from congenital œsophageal stenosis:

1. There is a history of vomiting from birth or shortly after birth The vomiting may be related to position (being less in the upright position), but this has not been found to be entirely reliable.

2. There may be hæmatemesis during infancy.

3. Radiological examination before the occurrence of the secondary stenosis will show an abnormal gastro-œsophageal reflux. It may or may not be possible to identify a diaphragmatic hiatus hernia at any one examination. The reflux will at times continue after the development of stenosis, the gastric contents washing from stomach into œsophagus and through the stenosis into the upper œsophagus and even pharynx. This may occur even if the stenosis is severe enough to cause difficulty in deglutition.

4. The area of stenosis itself, as shown by x-ray examination, may be irregular in contour, and may even show ulcer niche formation.

5. Œsophagoscopy will usually show inflammatory changes in the region of the stenosis, and possibly proximal and distal to it.

6. Œsophagoscopy may show a hiatus hernia with a portion of the stomach above the level of the diaphragm.

7. If thoracotomy is done, the lesion will show changes of inflammation involving the œsophagus and, likely, the peri-œsophageal tissues.

8. Thoracotomy may show laxity of the diaphragmatic œsophageal hiatus, or hiatus hernia, or both.

9. Gross and microscopic examination of the lesion, if biopsy (or resection) is done, will show changes which are predominantly those of inflammation and fibrosis.

CONGENITAL ŒSOPHAGEAL STENOSIS

Although several types have been described, there appear, in general, to be two main types.[4, 11, 12, 34]

1. *Membranous.*[8] At any level in the œsophagus, but particularly at

its upper end, at the level of the tracheal bifurcation, or in the lower third, a web or diaphragm may be present. This is thin and well defined, and appears to consist in an infolding of mucosa and sub-mucosa. The experience of others has suggested that one or more dilatations are usually sufficient to produce a good result. Its opening varies in size and is usually central, but occasionally eccentric openings have been reported. The single case reported by Abel in 1929 is the only one in the available French and English literature of an imperforate œsophageal membrane.[1, 2]

2. A *localized thickening of the œsophageal wall involving submucosa and muscularis.*[17] It varies from a few millimeters to approximately 1.5 cm. in length. The commonest location is just below the tracheal bifurcation and in the lower third of the œsophagus.

In the assessment of œsophageal stenosis the following suggest a congenital origin:

1. The vomiting usually begins with the ingestion of semi-solid or solid food, rather than at birth.
2. There is no history of hæmatemesis.
3. Radiological examination will not show gastro-œsophageal reflux of constant or significant degree, and will not show diaphragmatic hiatus hernia.
4. The area of stenosis will be well defined. It may be of the membranous (diaphragm or web) type or of the longer (fibromuscular) type. Occasionally, as in cases I and IV, there appears to be a double narrowing with a relatively normal œsophageal segment between.
5. The stenosis is smooth and regular, and there is no suggestion of ulcer niche formation.
6. Œsophagoscopy does not show any significant inflammatory change in the mucosa at or near the lesion.
7. Œsophagoscopy does not show a diaphragmatic hiatus hernia.
8. Thoracotomy, if done, does not show any inflammatory change in the œsophagus or peri-œsophageal structure.
9. Pathological examination shows a well-defined lesion with predominantly fibromuscular thickening. Pathological examination of the membranous or web type has not been reported frequently or fully.[4, 6, 11]

DEMONSTRATION OF THE LESION

It seems likely that the reported low incidence of congenital œsophageal stenosis is less than the actual incidence, partially because the lesion is sometimes not recognized. We believe it important to use a catheter in outlining the lesion, and the œsophagus immediately below

it, when œsophageal stenosis is suspected or diagnosed. When stenosis is suspected, the catheter will, by distending the œsophagus at this point, clearly show the lesion and its length.

It should be noted that a soft rubber catheter or fine polyethylene tube is used. No attempt is ever made to force it past the point of obstruction. We have been greatly helped, when the lumen is markedly reduced by the stenosis, by insertion of the tube under direct vision of the œsophagoscopist. Injection of the opaque medium, when a stenosis is diagnosed, allows clear definition of the lesion, its length and contour, and the œsophagus distal to it. It seems likely from the literature on primary and secondary stenosis that many cases are thought to be longer than they actually are because the stenosis allows only a fine trickle of barium to enter the distal œsophageal segment, which, since it is collapsed, resembles a long stenotic area. In addition, when the distal segment is distended by injection, one can study its peristalsis. This is valuable in demonstrating or excluding a hiatus hernia, since œsophageal peristalsis is usually distinguishable from gastric peristaltic activity. The catheter can, when through the stenosis, also be used to fill the stomach with opaque medium, and gastro-œsophageal reflux can be demonstrated or excluded by appropriate positioning and fluoroscopic observation.

Schatzki[27] pointed out that in the identification of "lower œsophageal ring" the lesion had likely been missed in the past, because the œsophagus had not been examined in the distended state. He made use of the temporary arrest of the œsophageal bolus at the cardia in the normal adult during forced inspiration. This distends the lower segment and allows the "ring" to be clearly shown. In infancy it is, of course, impossible to have the patient hold his breath in inspiration, but a catheter will distend the œsophagus and similarly allow adequate study.

TRACHEO-ŒSOPHAGEAL FISTULA

Case III showed a tracheo-œsophageal fistula associated with œsophageal stenosis. The much commoner association of tracheo-œsophageal fistula with œsophageal atresia is now well known.

Case III, together with occasional similar reported cases[12] of œsophageal stenosis at or just below the tracheal bifurcation associated with tracheo-œsophageal fistula, indicates that identification of a stenosis in this area should promote most careful search for an associated fistula. This is particularly true since a history of dysphagia and choking on feeding could well be explained away as due to the stenosis alone in such a case. The usual difficulties of diagnosing tracheo-œsophageal

fistula when not associated with œsophageal atresia have been fully recorded in recent years.[10, 34]

DIFFERENTIAL DIAGNOSIS

The *"lower œsophageal ring"*[27] is now a well-known phenomenon in adults. Its ætiology is still not clear. It may either be congenital or be secondary to or associated with hiatus hernia, as noted by Schatzki and Gary. To date, in view of the relatively mild symptoms produced, insufficient endoscopic and pathological examinations are available to permit clarification. It is possible that some of these are, in fact, mild cases of congenital œsophageal stenosis. We know no way of distinguishing these two lesions, except by their age incidence or natural history.

Cardiospasm (achalasia) in infants is exceedingly rare. Occasional reports are available in the literature, but are hard to assess.[4] If it occurs in infancy, it would be difficult to distinguish from congenital œsophageal stenosis. The identification of cardiospasm would presumably be dependent upon the same criteria as those which obtain in the adult, i.e., a smooth, tapering distal œsophageal narrowing, showing intermittent partial relaxation and allowing the œsophageal content to enter the stomach intermittently in spurts, and without a well-defined muscular or fibromuscular stenosis, which can be identified at operation or pathological examination.

Secondary (cicatricial) stenosis has been discussed above.

"Œsophageal web" in the lower segment has been reported as possibly a separate lesion.[6, 7] The description of these webs does not suggest that it differs in any respect from the "membranous" type of congenital œsophageal stenosis, which can occur at any level in the œsophagus.

SUMMARY AND CONCLUSIONS

Five cases are reported which are thought to be due to congenital œsophageal stenosis.

Of these, one was just below the level of the tracheal bifurcation and was associated with a high tracheo-œsophageal fistula.

Of the others, two had surgical resection of the lesion and pathological study of the resected specimen.

It is suggested that congenital œsophageal stenosis may not be as rare as has been commonly supposed.

When œsophageal stenosis is suspected, it can be clearly demonstrated by the gentle injection of radio-opaque medium proximal to,

and especially distal to, the site of the lesion. This method appears to improve diagnostic accuracy.

Differentiation from other abnormalities, and in particular from stenosis secondary to gastro-œsophageal reflux with peptic œsophagitis, should be made, using the following criteria: (1) vomiting, or dysphagia, or both, beginning, not at birth, but at the time solid food is first added to the diet; (2) demonstration by radiological means and by other means where applicable (endoscopy, thoracotomy) of a clearly defined, usually short, stenosed segment, without evidence of gastro-œsophageal reflux, hiatus hernia, œsophagitis, œsophageal ulcer or peri-œsophagitis; (3) when pathological examination is obtained, gross and microscopic findings of a predominantly fibrous or fibromuscular thickening with slight or no inflammatory reaction.

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VERTEBRAL ANOMALIES AND ALIMENTARY DUPLICATIONS

Clinical and Embryological Aspects

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The occurrence of four cases with a posterior mediastinal cyst, an anomaly of the cervico-dorsal spine and intestinal duplication, and three cases showing the spinal anomaly and posterior mediastinal cyst only, has precipitated the presentation of the data included in this report. These cases occurred on the Surgical Service of The Montreal Children's Hospital (formerly The Children's Memorial Hospital, Montreal, Canada). These cases would appear to support a new concept in the embryogenesis of intestinal duplications and emphasize an important clinical entity to the pædiatrician and children's surgeon.

CASE REPORTS

Case I. M.N., a male infant aged 5 months, was admitted to The Montreal Children's Hospital April 7, 1953. This infant presented with the history of not feeding well, failure to gain weight, and the passage of blood *per rectum* intermittently for 3 months. The patient was dyspnœic and cyanosed. Physical examination revealed a dorsal scoliosis, convex to the left, with definite indrawing of the lower thoracic cage. The head was held with the neck extended. There was dullness to percussion over the right hemithorax.

Radiological examination of the chest (Fig. 35) showed hemivertebræ at D 3 and D 7 producing the scoliosis. A large spherical mass was present in the right posterior thorax at the level of D 7. The right lung showed over-æration. The left lung was compressed by the right lung and the displaced mediastinum.

Operative Findings. A right thoracotomy through the fifth right interspace was performed. A thick-walled cystic structure was visualized in the right posterior medias-

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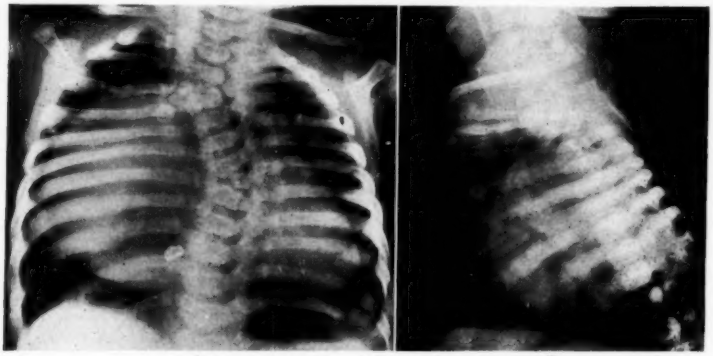
tinum, covered by mediastinal pleura, crossed by the azygos vein and closely adherent to the œsophagus anteromedially and the vertebral body posteriorly. The cyst was removed and the thorax closed with underwater-seal intercostal drainage. The post-operative course was stormy, and the baby experienced persistent respiratory distress with cyanosis. While the infant was being readied for endotracheal suctioning, cardiac arrest occurred. It was impossible to resuscitate the infant. Death occurred 24 hours after operation.

Pathological Report. The specimen consists of a cyst measuring 5 by 3.6 by 2 cm. that is smooth, glistening and hæmorrhagic on the external surface. One pole of the cyst is thick and firm. The wall measures 1.8 cm. in thickness and contains a smaller cyst in its substance. The cyst contains 60 ml. of straw-coloured fluid. The lining of the large cyst is smooth, shining and red with a few areas of mucosa present. The wall shows muscle and fibrous tissue bands. The smaller cyst measures 1.5 by 1 cm. with



A B

Fig. 35. A, Anteroposterior x-ray of chest showing hemivertebræ at D 3 and D 7—scoliosis. A large spherical mass occupies the right hemithorax. *B*, Lateral x-ray of chest showing cyst in posterior thorax.

a slit-like lumen lined by velvety mucosa. Histologically, the large cyst is composed of a lamina propria, muscularis mucosæ, a submucosa and outer muscularis, and a few areas of intestinal type of mucosa. Most of the lining is scar tissue. Granulation tissue is prominent in the lamina propria and submucosa, together with areas of old and recent hæmorrhage. The small cyst is similar in structure and is lined by gastric epithelium.

Autopsy Findings. The following gastro-intestinal tract anomalies were found. A reduplicated segment of bowel arises from the mid-ileum and extends proximally for 16 cm. in the mesentery of the ileum. It abruptly narrows down to a fibrous cord which follows a branch of the mesenteric artery to a point beneath the head of the pancreas. The lumen of this duplication is filled with blood. The wall is intact throughout, and microscopically is seen to be lined by gastric mucosa. A small sealed perforation is present at the junction of ileum and duplication. Arising from the ileum 45 cm. proximal to the ileocæcal valve is a Meckel's diverticulum, which is entirely lined by ileal mucosa.

Case II. B.R., a male child aged 9 years, was admitted to The Montreal Children's Hospital March 6, 1953. The patient had had 6 to 8 episodes of acute epigastric pain daily for several years. In 1947 he was investigated for recurrent abdominal pain, and in 1951 he had a cystic tumour removed from the right posterior mediastinum through a right thoracotomy at another hospital (Fig. 36). On his first admission to The Montreal Children's Hospital he was described as a thin, pale child, weighing

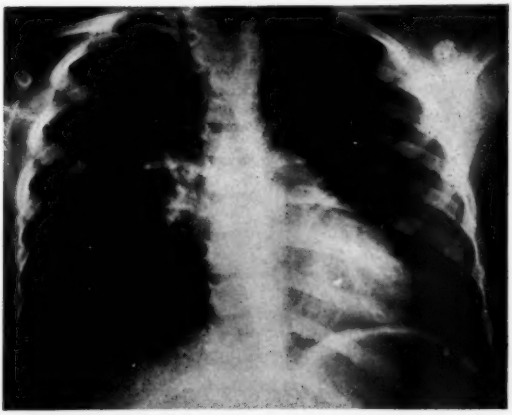


Fig. 36. Anteroposterior x-ray of chest showing cystic mass in right hemithorax.

Fig. 37. Barium series showing considerable distortion of one loop of jejunum, suggesting a long, irregular mass protruding into the lumen of the jejunum.

37½ pounds, and there were no significant physical findings. The x-ray report of a barium series (Fig. 37) stated that there was considerable distortion of one or 2 loops of jejunum suggesting a long, irregular mass protruding into the lumen of the jejunum. Changes in the upper dorsal spine were reported as those of under-segmentation. No definite diagnosis was arrived at, and as the symptoms subsided the patient was discharged from hospital. The patient was readmitted on April 11, 1953, just 4

days after the patient of case I, in a state of profound shock, with pallor, dyspnœa and a hæmoglobin of 1.5 gm. Examination of the abdomen revealed a board-like rigidity. After the administration of 500 ml. of whole blood and 800 ml. of packed red blood cells a laparotomy was performed.

Operative Findings. An intramesenteric duplication of the mid-jejunum was found and resected. The duplication measured 36 cm. in length and was resected with the adjacent bowel. End-to-end anastomosis of the jejunum was effected. The patient's post-operative course was uneventful, and he was discharged home on the seventeenth post-operative day.

Pathological Report. Posterior Mediastinal Cyst.* The specimen consists of a cyst measuring 5.5 by 2.5 cm. It contains a creamy white liquid. The wall is lined by stratified, ciliated columnar epithelium (Fig. 38). This finding is compatible with the fact that embryonic œsophageal mucosa is lined by columnar epithelium, much

Fig. 38. Cyst with inner lining of pseudo-stratified columnar epithelium with cilia, a submucosa and outer thick muscular layer. Hemalum phloxin saffron. × 10.

of which is ciliated.[2, 20, 21] There is a submucosa and muscularis mucosæ, and the ganglionic plexuses are present in the muscular layers.

Jejunal Duplication. The specimen consists of 25 cm. of small bowel and attached mesentery. The proximal 10 cm. are thick-walled with a dull serosa covered by yellowish fibrinous exudate. There are 2 punched-out perforations 0.3 and 0.5 cm. in diameter. The mucosal surface of the first 5 cm. is small bowel in type. Beyond this there is a large area of gastric type of mucosa. The perforations lie in the small bowel mucosa at the edge of this gastric mucosa and have the microscopic appearance of peptic ulcers. Externally, at the 10-cm. level of the small bowel, a narrower, hollow tube arises from it and lies closely approximated to it, between the leaves of its mesentery. Internally, this smaller tube communicates with the larger through an ostium 0.9 cm. in diameter, which lies in the midst of the gastric mucosa described in the small bowel. This gastric mucosa passes through the ostium and lines a small area surrounding the ostium. The remaining portion of the main loop is not remarkable and is lined by ileal mucosa. The duplication is about 16 cm. in length. It is 2 cm. in width for the first 9 cm., and at this level there is a stricture which has a circumference of 1 cm. The mucosa is ulcerated here over an area of 1.5 cm. in length, and

* We are indebted to Dr. L-C. Simard, Director, Department of Pathology, Hôpital Notre Dame, Montreal, for this information.

the edges overhang the ulcer. There is a 0.3-cm. clean-cut perforation in the ulcer base. The distal 6 cm. of the duplication are dilated to a circumference of 5 cm. and are thin-walled. It ends blindly without finding communication with the bowel, although the separation between them is thin, consisting of only a few muscle layers. Microscopically, the duplication is lined by gastric mucosa, and the ulcer is compatible with peptic ulceration.

Case III. S.B., a female infant aged 5 months, was admitted to The Montreal Children's Hospital June 9, 1953. The patient was well until 15 days before admission,

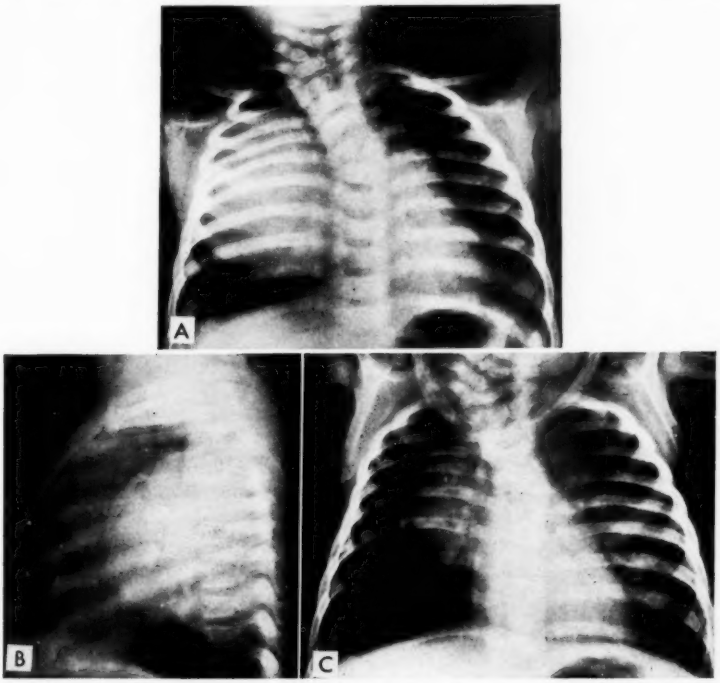


Fig. 39. A, Anteroposterior x-ray of chest showing large mass in right hemithorax and anomaly of the upper dorsal and cervical spine. *B*, Lateral x-ray of chest showing cystic mass in posterior mediastinum. *C*, Anteroposterior x-ray of chest showing reduction in size of cyst after aspiration of 60 ml. of bright yellow non-viscous fluid.

when she became dyspnœic, restless and anorexic. She was treated for pneumonia and improved slightly, but the dyspnœa persisted. In the hospital she was cyanotic with rapid, noisy respirations. Physical examination revealed that the right hemithorax moved less than the left and that there was dullness over the right apex anteriorly and the whole upper half posteriorly. There was indrawing over the lower thoracic cage. A dorsal scoliosis convex to the left was noted. X-ray examination (Fig. 39, *A*, *B*) showed a large mass in the posterior mediastinum, associated with an anomaly of the upper dorsal and cervical spine, comprising hemivertebræ. The right lung was over-ærated. Because of respiratory distress, aspiration of the cyst was carried out under local anæsthesia. Sixty milliliters of bright yellow, non-viscous fluid were aspirated with improvement of respiration (Fig. 39, *C*). The over-æration of the right lung persisted, however.

Operative Findings. Through a right thoracotomy a large, smooth-walled cystic mass was found in the right paravertebral gutter, covered with the mediastinal and parietal pleura. The azygos vein crossed the structure. One long fibrous stalk was adherent posteriorly to the body of the vertebra. The cyst was removed, and the patient's post-operative course was uneventful. She was discharged on the twelfth post-operative day. Stool examination was negative for occult blood. Barium series failed to show any evidence of duplication of the small intestine, and a 4-year follow-up found the child well, with no history of melena.

Pathological Report. The specimen consists of a cyst measuring 5 by 4 by 2.5 cm. Half the wall is rather firm, the other soft and rubbery. On section 2 cysts are seen separated by a thin wall. The walls vary from 0.4 to 1 cm. in thickness and have a varicoloured, rough inner surface. Some thick grumous material is present in the

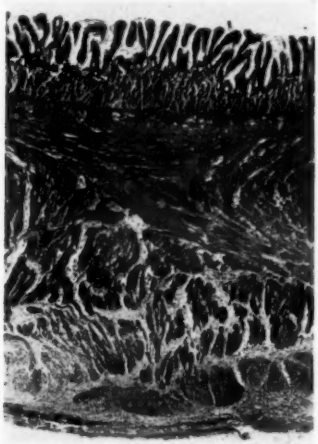


Fig. 40. Cyst showing characteristic gastric mucosa. At the top of the photograph is a mucous-secreting layer, beneath which lies the glandular zone with parietal cells. Externally there is a thick muscular coat. Hemalum phloxin saffron. × 20.

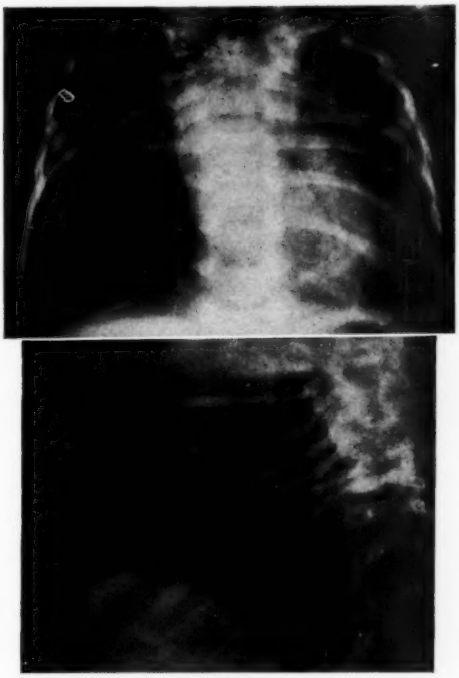
larger cyst. Microscopically, there is an outer connective tissue layer. Inside this there is a thick muscular coat with 2 and sometimes 3 layers which show focal scarring. Inside this there is a submucosa and muscularis mucosæ. The lining is sometimes typical gastric mucosa (Fig. 40), and sometimes granulation tissue containing chronic inflammatory cells and foci of foamy macrophages. A myenteric plexus is present.

Case IV. J.T., a male infant aged 1 month, was admitted to The Montreal Children's Hospital October 22, 1953. For 3 days before admission the infant had had 5 to 6 cyanotic periods daily lasting up to 30 minutes. Physical examination revealed a well-developed and well-nourished male infant in respiratory distress. There was definite subcostal indrawing. The respiratory rate was 56 per minute. Breath sounds were markedly diminished over the right side. X-rays (Fig. 41) showed a large spherical mass in the right upper mediastinum, lying posteriorly and markedly displacing the œsophagus anteriorly. There was a gross anomaly of the dorsal vertebræ from D 2 to D 6. They were underdeveloped and partially fused.

Operative Findings. In the operating room an attempt was made to aspirate this cystic mass before the chest was opened, but no fluid was obtained, and so the thoracotomy was proceeded with. A cystic mass, measuring about 5 by 2.5 cm., was found lying in the right paravertebral gutter and covered by parietal pleura. No

azygos vein was seen. The mass was dissected out until only a pedicle about 3 mm. in diameter remained, adherent to the left side of the vertebral body of the fifth dorsal vertebra. The cyst was opened, and the pedicle could be probed for a short distance into the vertebral body. The pedicle was then severed, and the probe entered only a few millimeters into the body of the vertebra. The post-operative course was complicated by a left upper lobe atelectasis and a collection of fluid on the right side of the thorax, but these resolved under therapy, and the patient was discharged on the

A



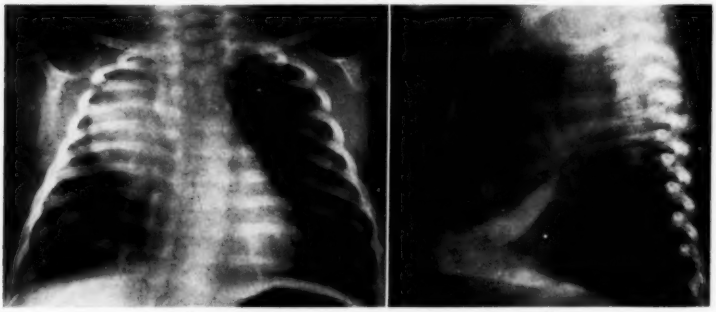
B

Fig. 41. *A*, Anteroposterior x-ray of chest showing cystic lesion in upper right hemithorax with severe anomalies of vertebrae D 2 to D 6. *B*, Lateral x-ray of chest showing cyst in posterior mediastinum.

fourteenth post-operative day. Examination of the stool was negative for occult blood, and subsequent barium series showed no evidence of an intestinal duplication.

Pathological Report. The specimen consists of a cyst 2.5 cm. in diameter. It had been opened and emptied of its contents. The external surface is mottled grey and red. The wall is about 0.4 cm. in thickness. The lining is varicoloured with a few areas resembling mucosa. Microscopically, there is a serosa showing fibrosis and slight chronic inflammation. A muscular coat is present with 3 layers in some places and focal fibrosis in others. There is a submucosa and muscularis mucosæ. The lining is formed by granulation and scar tissue in many sections, and in one area by gastric mucosa.

Case V. G.C., a female infant aged 2 months, was admitted to The Montreal Children's Hospital February 22, 1955. The infant had experienced difficulty in breathing for one week before admission. The baby had had a cough since birth with several bouts of cyanosis. There was no difficulty in feedings. Physical examination revealed some dullness over the right thorax posteriorly and some decreased breath sounds in this area. Chest x-rays (Fig. 42) from the referring hospital showed a mass situated in the right posterior thorax associated with anomalies of the upper thoracic vertebræ. There was also some collapse of the right middle lobe and some emphysema of the right lower lobe. Later films showed complete collapse of the right middle lobe and less emphysema of the right lower lobe. The mass in the right upper posterior mediastinum was spherical, well defined, and situated in the paravertebral gutter. It was associated with incomplete segmentation of the third and fourth thoracic vertebræ, and asymmetry of development of the third, fourth, fifth and likely sixth thoracic vertebræ. Examination of the intestinal tract did not reveal any evidence of an abnormality of the small bowel, and in particular that of a duplication.



A B

Fig. 42. A, Anteroposterior x-ray of chest showing mass in right upper posterior mediastinum and dorsal vertebral anomalies. B, Lateral x-ray of chest showing posterior position of cyst and collapse of right middle lobe.

Operative Findings. On March 1, 1955, a posterior mediastinal cyst was removed through a right thoracotomy. The chest was closed without drainage. The post-operative course was complicated by pneumonia, but the patient was discharged on the nineteenth post-operative day.

Pathological Findings. The specimen consists of a cyst 4.5 by 3.5 by 3.2 cm. with a mottled external surface containing hæmorrhagic areas. It contains 25 ml. of a slightly cloudy whitish fluid. The wall is of an irregular thickness and is composed of serosa, 2 outer muscle coats, submucosa and muscularis mucosæ. A small area is covered by gastric type of mucosa, while the remaining surface is ulcerated. The submucosa and serosa are œdematous with areas of hæmorrhage and mild round cell infiltration.

Case VI. C.L., a male infant aged 3 months, was admitted to The Montreal Children's Hospital February 21, 1939. This infant had been vomiting, and there was an inability to feed well since birth. A cough had been present for one week. The vomiting was not projectile and appeared to follow feedings. There was definite dullness over the right posterior thorax, and the breath sounds were diminished over the same area. A barium series was done and revealed no evidence of congenital hypertrophic pyloric stenosis. Films of the chest (Fig. 43) revealed a rounded shadow occupying the posterior portion of the chest, extending from the level of the diaphragm upward to the level of the second interspace anteriorly. This mass reached within 2 cm. of the anterior chest wall and extended to the lateral chest wall. It was of a homogeneous

density throughout. More films were made after the aspiration of 2 ml. of fluid and the injection of 10 ml. of air into the mass. This examination suggested that the mass was partially cystic. This procedure was repeated, the same conclusions being reached. After this, 25 ml. of fluid were withdrawn and replaced with air. This suggested that most of the mass was cystic and now contained air and fluid. A barium swallow was then performed, and the slow emptying of the stomach was attributed to an unusual situation of the small bowel, particularly in its proximal portion. Vomiting diminished, the patient's condition remained the same, and he was discharged on April 5, 1939.

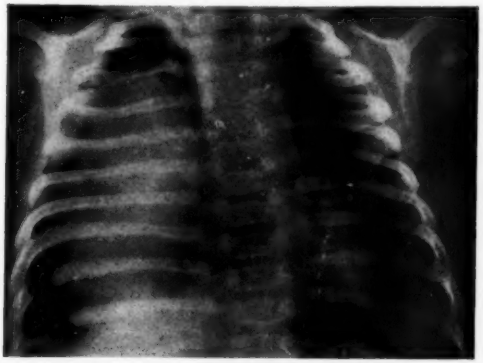


Fig. 43. Anteroposterior x-ray of chest showing rounded shadow occupying the right hemithorax from the second interspace to the level of the diaphragm.

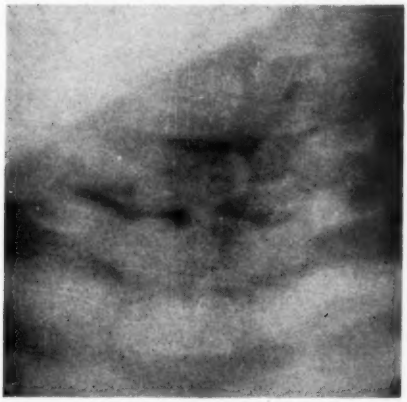


Fig. 44. X-ray of lower cervical spine showing partial fusion and incomplete segmentation of the vertebral bodies.

On April 16, 1939, the patient was readmitted with an interval history of vomiting after meals and of anorexia. On April 22, 110 ml. of fluid were removed from the cyst, and on April 27, 90 ml. of fluid were aspirated. On May 5, 120 ml. were removed from the cyst. On May 6 and 7 the baby experienced periods of profound respiratory depression and cyanosis, and expired on May 8, 1939. Revision of the x-rays of the chest revealed an abnormality of the lower cervical spine (Fig. 44) with partial fusion and incomplete segmentation of the vertebral bodies.

Pathological Report. On opening the chest, the heart was shifted to the left, and the right lung was flattened against the anterior chest wall. The major portion of the right thorax was occupied by an extrapleural cyst 9 by 6 by 7 cm. in size. This cyst communicates by an 0.8-cm. tube passing behind the diaphragm to a paraduodenal cyst 3 cm. in diameter (Fig. 45). This cyst lies in the mesentery of the duodenum, which was present in this case. This in turn communicates by a tiny opening with a wide channel, opening into the third part of the duodenum. This series of cysts and tubes represent a duodenal duplication. The thoracic cyst contained 150 ml. of milky fluid, was multiloculated and contained areas of gastric mucosa and of intestinal mucosa. Areas of squamous epithelium were seen. Some of the surface was ulcerated and showed a chronic inflammatory reaction. The remaining thickness of the wall was

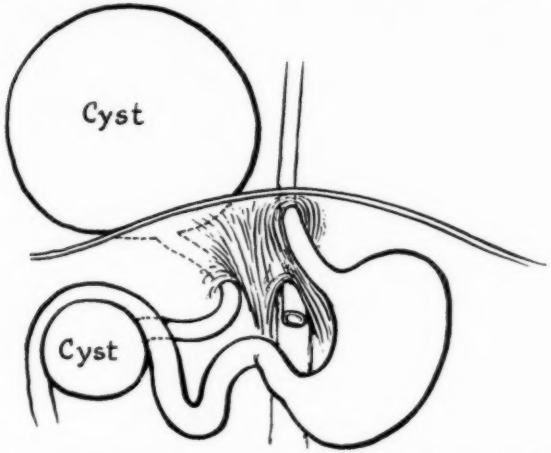


Fig. 45. Schematic drawing showing thoracic cyst (*top*), diaphragm, paraduodenal cyst and the connecting tube. The latter passes behind the right crus of the diaphragm and behind the second part of the duodenum.

formed of muscle in 2 layers, a submucosa and a serosa. The tube connecting the thoracic cyst to the paraduodenal cyst is composed of 2 muscle layers and a mucosa of gastric type. At 2 points in the wall a small focus of glial tissue was seen, associated with traces of pia-arachnoid and clusters of melanin pigment-containing cells (Fig. 46).

Case VII. C.C., a male infant aged 3 months, was admitted to The Montreal Children's Hospital November 6, 1945. Three weeks before admission the patient had been admitted to another hospital because of excess mucus and respiratory distress. The patient was discharged 3 days later, improved. A week later he was again admitted to the same hospital with the complaint of bleeding *per rectum*. Here he was given a transfusion of whole blood. Pneumonia developed from which he recovered, and he then was transferred to The Montreal Children's Hospital

The patient was a well-nourished but pale infant in no apparent distress. The chest was resonant throughout, and the breath sounds were normal throughout the chest. X-ray examination (Fig. 47) was done and revealed no evidence of obstruction or other abnormality except the presence of numerous fused vertebræ in the dorsal region with several hemivertebræ, and considerable reduction in the number of vertebræ.

Operative Findings. Laparotomy was performed, and a duplication of the ileum was removed along with 10 inches of the ileum; an end-to-end anastomosis was performed about 4 inches from the ileocæcal valve. He was discharged home on the thirteenth post-operative day.

The patient was readmitted to The Montreal Children's Hospital on December 4, 1945. Complaints now were cough since discharge and hæmoptysis of 4 days' duration. The cough was productive and contained flecks of dark red blood. There were dry, coarse *râles* throughout both lung fields. No gross area of consolidation was seen in either lung on x-ray. The patient responded well to sulfonamide therapy and was

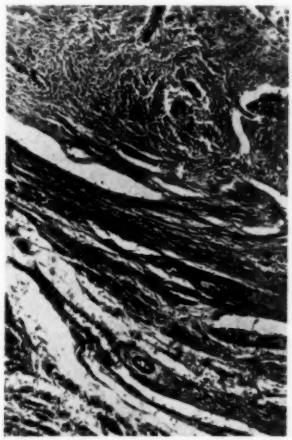


Fig. 46. The pale grey feltwork layer at the top half is glial tissue. The bottom half consists of dense collagen and areolar tissue. The central black streaks are melanin pigment. Hemalum phloxin saffron. × 100.

Fig. 47. Anteroposterior x-ray of chest showing numereous fused vertebræ in the dorsal region with several hemivertebræ and partially fused ribs.

discharged one week after admission. On January 19, 1946, the patient was again admitted to The Montreal Children's Hospital with hæmoptysis and coughing spasms, which were productive of a large amount of mucoid material. There was no significant fever at any time. Chest x-ray and bronchogram showed a radiolucent cavity transiently visualized behind the hilum of the right lung and a skeletal deformity reported as the "dorsal mass syndrome" with hemivertebræ. The child's condition deteriorated

slowly, and he was discharged home on February 2, 1946, as a case of multiple congenital anomalies. The patient expired on March 25, 1946.

Pathological Findings. The operative specimen consists of 20 cm. of ileum with attached mesentery. Lying in the mesentery is a duplication of the bowel arising from the ileum. The duplication is about 30 cm. in length with 2 saccular dilatations occurring in series in its distal portion. A large portion of the mucosa of the duplicated segment is gastric in type, especially in the saccular dilatations. One large and 3 small peptic ulcers are present in the mucosa of the duplication. The structure of the rest of the thickness of the wall is typical of the gastro-intestinal tract.

The duplication contained 73 ml. of fluid, which was examined chemically and showed 0.1 per cent concentration of free hydrochloric acid. The fluid digested milk and coagulated albumin, indicating the presence of both rennin and pepsin.

Autopsy was performed at an out-of-town hospital, and their record makes no mention of finding a posterior mediastinal cyst. There were adhesions binding the posterior and mediastinal surface of the lower lobe of the right lung to the chest wall and pericardium. This lobe was collapsed and partially fibrosed and showed a 0.5-cm. abscess near the mediastinal surface.

The available details leave some doubt as to whether this "abscess" was not a marsupialized mediastinal cyst opening into the lung. This doubt is strongly supported by the clinical history, which is compatible with that of a ruptured cyst.[15]

EMBRYOGENESIS

From the cases presented it would seem that one could find an embryological aberration from the normal that would explain the associated findings in the seven cases. This hypothesis must explain the formation of alimentary duplications, must associate their formation with the vertebral anomalies and explain the incorporation of central nervous tissue found attached to the wall of the cyst in case VI.

Von Wyss, in 1870,[30] first reported a posterior mediastinal cyst, and Roth, in 1881,[23] noted the posterior attachment of a mediastinal cyst to the vertebral column, together with an intramesenteric cyst with a ciliated lining and a duplication of the ileum. Leuss, in 1910,[13] restudied a case reported by Hennig in 1880[9] and reported the mediastinal cyst as foregut in origin.

Veeneklaas, in 1952,[29] theorized that if separation of the notochord from the entoderm was not complete, a diverticulum of entoderm could be withdrawn from the primitive foregut (archenteron) which would form a cyst, and the attachment of the cyst to the notochord could prevent fusion of the vertebral bodies, resulting in a spinal anomaly. Fallon *et al.*, in 1954,[6] discussed this theory and applied it to their report of two cases. However, Veeneklaas' theory cannot account for the presence of the central nervous system tissue found in close relationship to our cyst in case VI.

At the same time McLetchie, Purves and Saunders, 1954,[16] reporting on the genesis of gastric and certain intestinal diverticula and enterogenous cysts, reported a case similar to case VI. In a survey of 37 cases of anterior and/or posterior or combined spina bifida Saunders noted that a diverticulum or strand often passed from some part of the

alimentary tract toward the vertebral cleft and spinal cord and named this the 'neurenteric' diverticulum or strand. "Embryologically," Saunders[24] states, "the vertebral cleft and 'neurenteric' connections were accredited to the formation of a cleft notochord, and an ento-ectodermal adhesion that connected the developing gut with the neural tube." It is to be noted that in 1929 Feller and Sternberg[7] had developed the split notochord theory. The proposal of an ento-ectodermal adhesion could afford an explanation, then, for the central nervous system tissue found in case VI.

To understand the structure of the earliest human embryo, it is helpful to recall the presence of three primary germ layers (Fig. 48). The ectoderm forms the outer covering of the embryo and gives rise to the neural plate which forms the central nervous system. The ento-

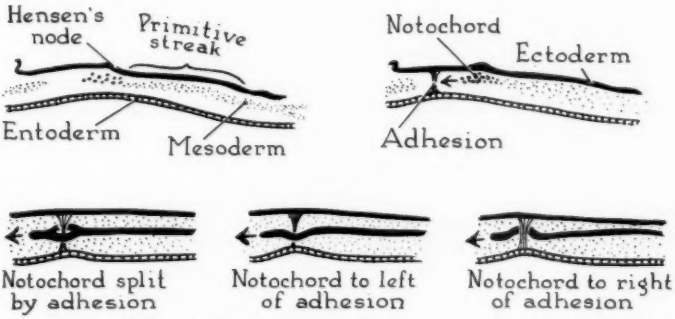


Fig. 48. Sagittal sections of the pre-somite human embryo (diagrammatic).

derm forms the primitive gut cavity or archenteron and gives the intestinal tract its mucosal lining. The mesoderm, which develops between the ectoderm and entoderm, gives rise to the vertebrate skeletal, muscular and circulatory structures.

Intimately associated with the general mass of mesoderm is the origin of an axially located cylindrical mass of cells known as the notochord. The cells of this structure take their origin from a thickened mass of proliferating cells known as Hensen's node at the anterior end of the primitive streak. Pushing cephalad, these notochordal cells become moulded into a characteristic rod-shaped mass. The sheet-like mass of mesodermal cells arising from the primitive streak, in their peripheral spread, seem to leave a temporarily vacant area just cephalad to the primitive streak, and it is into this unoccupied area that the notochord grows. This rod of notochordal cells is then enveloped by the paraxial cell mass of mesoderm which later segments to form the vertebral column, retaining the notochordal remnants as the nucleus pulposus of the intervertebral disks.

Figure 49 illustrates the normal process of enclosure of the spinal cord and notochord by the paraxial mesodermal cell mass to form the vertebral body by its anterior fusion ventral to the notochord and dorsal to the primitive gut. In the cephalic end of the pre-somite embryo the ectoderm or neural plate and the entoderm are in close proximity, with no intervening structures. An adhesion between ectodermal and entodermal germ layers may occur, and this adhesion may split or *divert* the cephalad growth of the notochord.

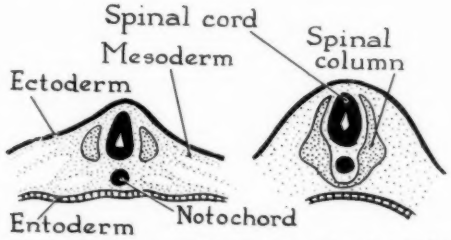


Fig. 49. Normal process of enclosure of the spinal cord and notochord in the formation of the vertebral body, in cross section. (After Arey, Brash and Keith.)

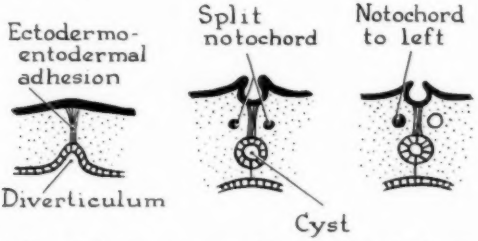


Fig. 50. Cross section of structures concerned in formation of a traction diverticulum and cyst, showing the split and deviated notochord.

Figure 50 shows a cross section of the structures concerned with the development of a diverticulum by traction and later the formation of a duplication if the neck of the diverticulum closes. The split or deviated notochord is shown. This illustrates also how the attachment of the cyst or diverticulum can be (1) midline on the vertebral body, (2) attached to the right side of the vertebral body or (3) attached to the left side of the vertebral body, all conditions which were present in our cases. If the paraxial mesodermal vertebral anlage cannot close completely anteriorly to form the vertebral body because it is interrupted in its fusion by the ecto-entodermal adhesion, then this results in a vertebral body defect around the adhesion. The adhesion thus becomes the attachment of the cyst posteriorly.

In 1955 Geoffrey Knight[12] published a report of a case of gastro-

cystoma of the spinal cord. In this case the lower and upper thoracic vertebræ showed hemivertebræ and partially fused vertebræ, as in our cases. Figure 51 shows the embryogenesis of the gastrocystoma of the spinal cord by the dorsal migration of a traction diverticulum of the entoderm. The ventral migration of ectodermal structures (glial and pia-arachnoid tissue) could account for these structures being incorporated in the wall of the cyst in case VI (shown on the right of Figure 51).

That anomalous adhesions can occur in this area is supported by Patten's[18] description of a fusion of the notochord to the neural tube in a six-week human embryo.

Fig. 51. Cross section of structures concerned in the development of the rare gastrocystoma of the spinal cord on the left, and the manner in which central nervous system tissue is incorporated in the wall of a cyst (case VI) on the right.

It seems probable, then, that this is a satisfactory explanation for the developmental anomalies seen in these seven cases. It would appear that all the duplications had their origin in a region of the foregut where the potentiality for œsophageal, gastric and enteric mucosa was present. This seems to occur in the region of the lower cervical and upper thoracic vertebræ, where anomalies arise on the basis of an ectodermal-entodermal adhesion in the 15-day-old embryo with aberration from normal of the cephalad growth of the notochord, resulting in a disturbance of its enclosure by the paraxial mesodermal vertebral anlage.

The resultant vertebral anomaly may not be massive. Indeed, if the adhesion is small or detaches after the formation of a diverticulum or cyst or if the deviation of the notochord is slight, the lesion may be minimal. Saunders[16] has emphasized that there may be considerable reconstruction to normality after the notochord has split. Veeneklaas[20] has stated that tomograms may be necessary to detect the vertebral anomaly. *Because of the elongation accompanying the growth of the embryo, the cysts (diverticula) may be considerably caudad to the vertebral lesion.* Thus the vertebral anomaly is not always present in the x-ray film of a chest or abdomen.

There are still some who hold that duplications which contain gastric-like mucosa are of vitelline origin, but in our first case there was an intra-mesenteric duplication of the ileum, which was attached to the inferior border of the pancreas by a fibrous band also coursing between the leaves of the mesentery. This was associated with a posterior mediastinal cyst and a vertebral anomaly. There was also a Meckel's diverticulum on the anti-mesenteric border of the ileum, and no intestinal tract should have more than one diverticulum of Meckel. Lewis and Thyng, in 1907,[14] described minute knob-like groups of a few epithelial cells appended to the alimentary mass, but these were rarely seen on the dorsal aspect of the primitive alimentary canal. Furthermore, all intestinal duplications are intra-mesenteric. In addition, this theory does not account for the associated vertebral anomaly, and neither does the recanalization theory of Keith[11] and Bremer.[5]

SUMMARY

Seven cases have been presented, all showing a lower cervical and/or upper thoracic vertebral anomaly with the following associated congenital alimentary abnormalities: Five cases show a proved posterior mediastinal "cyst," one of which shows an additional duplication of the ileum and one an additional duplication of the jejunum. A sixth case shows a duplication of the ileum, but the presence of a mediastinal cyst is open to doubt. Clinically, the evidence is strong for a spontaneous communication between such a cyst and the right lung, but the autopsy findings are inadequate either to deny or affirm its presence. The seventh case (case VI) shows a "cyst" above the diaphragm in continuity with a paraduodenal cyst, which in turn communicates with a duodenal diverticulum. From these seven cases certain conclusions are drawn regarding embryogenesis and clinical diagnosis.

1. *Embryological Aspects.* Evidence is presented that in the presomite embryo an adhesion may form between the ectodermal and entodermal germ layers, which may split or deviate the notochord. This results in the formation of vertebral anomalies, alimentary system traction duplications in the posterior mediastinum, between the layers of the mesentery or in both locations. This theory has been elaborated to account for the rare gastrocystoma of the spinal cord and the presence of central nervous system tissue in the mediastinal duplication of our case VI.

2. *Clinical Aspects.* Attention is directed to the following clinical points:

a. The triad of a vertebral anomaly in the lower cervical and upper thoracic region with posterior mediastinal cyst (or duplication) and intestinal duplication.

b. The indications for x-rays of the chest and careful examination of the vertebral column in every infant with melena of obscure origin.

c. The search for vertebral anomalies in children with hæmoptysis and excess mucus, as some posterior mediastinal cysts have eroded into a bronchus.

d. The diagnosis of posterior mediastinal masses, if associated with vertebral anomalies, as cysts of foregut origin.

e. Cases showing Klippel-Feil syndrome, anterior spina bifida, posterior spina bifida, congenital scoliosis, hemivertebræ, under-segmentation, under-development or partial fusion of the cervical or dorsal vertebræ should be screened for the presence of neural or alimentary anomalies, or both.

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GENETIC COUNSELLING IN SOME COMMON PAEDIATRIC DISEASES

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The parents of a child with a particular disease may ask their pædiatrician about the possibility that the same disease might occur in subsequent children, the child's children, or other relatives. Often the information that the pædiatrician must have in order to answer such questions correctly is not easily available. The present article is intended to summarize and interpret such information about a number of the commoner pædiatric conditions, and also to indicate how inadequate the relevant data are, in some cases, and how cautiously they must be interpreted to the parents.

The author has discussed elsewhere[15, 17] the many considerations, other than the statistical risk of recurrence, that must be dealt with in genetic counselling. In the present paper, discussion will be limited to the probability of recurrence of the diseases considered, in siblings and other relatives of affected children. No attempt will be made to evaluate the evidence for or against specific genetic mechanisms underlying the diseases in question.

It is sad, but true, that the more common a disease is, the more difficult it is to provide accurate and helpful risk rates for genetic counselling. Diseases showing simple Mendelian inheritance, for which precise estimates of risk rates for relatives can be given, are almost always rare, presumably because of the strong pressure of natural selection against them. A list of such conditions of pædiatric interest has been presented elsewhere.[15] The commoner "constitutional" diseases tend to be ætiologically heterogeneous. They may contain in the same clinical category some cases with a strong genetic component,

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some almost entirely environmentally determined, and a wide variety of intermediate combinations, but there is usually no way of telling which is which. This makes genetic counselling difficult, since rates of recurrence used for counselling are statistical averages. They are derived by collecting, in one way or another, a series of families in which a case of the disease has appeared, and measuring the frequency of the disease in various categories of relatives. Such a series is, for the reasons just stated, an ætiologically heterogeneous collection, in which individual risks for siblings may vary from 0 to 50 per cent, with an average somewhere in between. Thus a counsellor may be dealing with a case in which the *average* risk that the disease will occur in a subsequent child is, say, 5 per cent, but he does not know whether the *actual* risk for this particular family is 50 per cent, 0, or some intermediate figure.

This state of affairs is so unsatisfactory that some authorities would prefer not to have risk rates published at all, arguing that readers may remember the average figures, without remembering the "ifs" and "buts," and, in using them, may convey a false sense of their reliability. There is something to be said for this point of view, but it can also be argued that the figures presented here, inadequate as they may be, are better than no figures at all or than grossly false ones. We have therefore extracted from the literature and our own records, information relating to counselling risks for a number of pædiatric conditions about which the pædiatrician is likely to be asked. In using the figures presented below, it should be kept in mind that establishing the statistical risk of recurrence is only the first step in the counselling procedure. Once established, the risk rates must be considered in relation to the emotional, social, economic and religious attitudes of the parents.[17] Predictions regarding possible occurrence of the disease in other members of the family should be interpreted to the parents with tact and sympathy and, if at all possible, by personal interview.

ANENCEPHALY AND SPINA BIFIDA APERTA

Our knowledge of the ætiology of anencephaly and spina bifida aperta (including meningocœle, myelomeningocœle and craniomeningocœle) is distressingly scanty. Penrose[41] lists eight different genetic hypotheses that have been involved to account for the familial distribution of anencephaly, all of them more or less unsatisfactory. Estimates of the incidence among babies born in hospital range from 0.012 per cent in Lyons to 0.671 per cent in Belfast.[41] Since anencephaly and spina bifida aperta occur within the same sibship more often than would be expected by chance, it would appear that they are causally related. Several workers[6, 39, 45, 46] have published series of cases more

or less suitable for analysis to determine the frequency of affected babies in the siblings of babies with such malformations. A similar series is accumulating in this Department.[34]

When the propositus has *anencephalus*, estimates of the frequency of anencephalus and/or spina bifida aperta in the siblings range from about 2 per cent[46] to about 7 per cent.[39, 45] When the propositus has *spina bifida aperta*, the frequency of anencephalus and/or spina bifida aperta in the siblings is about 3 per cent.[39, 45, 46] For easy memorization, a figure of 5 per cent would seem suitable for counselling parents of a child with either malformation concerning the probability that a subsequent child will be affected with one or the other defect, or both. However, in our (relatively limited) experience, we cannot escape the impression that occasional mothers (so far indistinguishable on genetic or clinical grounds) have a strong predisposition to bear children with axial system defects, and that in these cases the counselling risk is far above that for the majority of families.

In an effort to test this impression we have attempted to select, from the available data,[34, 39, 45, 46] those families in which the mother has given birth to two babies with anencephaly or spina bifida aperta, and to measure the frequency of these defects in subsequent children. Unfortunately, the data are scarce. Of 22 children born after two children with axial system defects, two were similarly affected, a frequency of 9 per cent. However, the numbers are so small that no definite conclusions can be drawn, except that the risk of having a child with an axial system defect after having already had two such malformed children is probably not, on the average, more than double the risk after having had one such malformed child; i.e., it is probably not more than about 10 per cent, in most cases.

In summary, when parents have had a child with an axial system defect, i.e., anencephalus or spina bifida aperta (including meningocœle, myelomeningocœle and craniomeningocœle), the risk of having another child with an axial system defect is about 5 per cent, on the average, but in a few cases it may be much higher than this. If they do have another such malformed child, the average risk of having a third is not very much greater than 5 per cent, though in occasional families it is probably quite large.

CLEFT LIP AND/OR PALATE

The literature on the ætiology of harelip and cleft palate is exhaustive, and cannot be reviewed here. For purposes of genetic counseling it is useful to keep the following facts in mind:

1. The general category of cleft lip and/or cleft palate contains many ætiologically different types. There is, for instance, a rare type asso-

ciated with accessory salivary glands of the lower lip, for which an autosomal gene with variable expressivity seems to be responsible.[54, 56, 59] It is said that the gene associated with mandibulo-facial dysostosis may produce cleft palate as one of its many end-effects.*

2. Cleft lip (with or without cleft palate) and cleft palate (without cleft lip) behave as different entities as regards their familial distributions. Thus the sibling of a child with a cleft palate has an elevated risk of having a cleft palate, but the probability of his having a cleft lip is not elevated. This is an encouraging bit of information to parents of a child with cleft palate, who tend to think of cleft palate as being associated with harelip, and to regard harelip as a more serious defect than cleft palate.

3. Although both cleft lip and cleft palate show a familial tendency, there is also an important but little understood group of environmental factors involved. Some progress has been made in sorting out these factors in experimental animals,[18] but the possibility that the experimental results are applicable to human beings has not been adequately tested, and should be regarded sceptically until it has. The fact that large doses of cortisone, injected into pregnant mice, of appropriate genotypes, at certain stages of gestation, may cause cleft palates in the offspring does not necessarily mean that cleft palates can be caused by corticoid therapy of pregnant women (although case reports of babies born with cleft palates following maternal treatment with cortisone[11, 22] require us at least to admit the possibility of a causal association in some cases). Because the question sometimes comes up in counselling, it might be mentioned here that the possibility of maternal "stress" during pregnancy causing cleft palates or other defects in the offspring by increasing the output of adrenal corticoids[55] or otherwise,[24] must be treated even more sceptically, since we are aware of no valid evidence to prove such a relationship. In the families we have interviewed so far the frequency of maternal "upsets" during pregnancy is the same in those pregnancies giving rise to babies with cleft lip and/or palate as it is in control pregnancies.

For counselling purposes, the risks may be considered according to the various situations encountered. Harelip, with or without cleft palate (CLP), and cleft palate, without harelip (CP), will be considered separately, since they appear to be separate entities.

Harelip, with or without Cleft Palate (CLP)

1. Parents Unaffected, One Child with CLP. According to Fogh-Andersen[13] and Fraser,[16] the average risk for each child of such parents lies between 4 and 7 per cent. For reasons discussed else-

* J. Warkany: Personal communication.

where,[16] the author considers Reed's[47] estimate of 14 per cent to be too high.

One might think that, if there was an affected relative (other than parent), the risk would be increased, but this does not appear to be so.[13, 16] Furthermore, the risk does not seem appreciably higher when the parents are related than when they are unrelated.

2. Parents Unaffected, Two Children with CLP. Little evidence is available relevant to this situation. From the combined data of Fogh-Andersen[13] and the author, it would seem that the frequency of CLP in children born to parents who have two children with CLP is about 10 per cent.

3. One Parent with CLP, No Affected Children. Fogh-Andersen[13] found that 2 per cent of the children of persons with CLP were similarly affected, and this seems a valid estimate for counselling in such situations.

4. One Parent and One Child with CLP. The average risk for other children of such parents being affected was estimated as about 14 per cent by Fogh-Andersen, but the combined data of Fogh-Andersen and the author give a value of 11 per cent. Because of the small numbers involved, this estimate is not to be regarded as precise.

Cleft Palate, without Cleft Lip (CP)

1. Parents Unaffected, One Child with CP. The risk of having a cleft palate is between 2 and 5 per cent for each child of such parents.[13, 16] Fogh-Andersen[13] found that when there was an affected relative (other than parent), the risk rose to 12 per cent, but pointed out that the numbers involved were small, and the estimate therefore unreliable. When the author's data are combined with Fogh-Andersen's, the risk of siblings of a child with CP, with normal parents but an affected relative, is only 6 per cent. It seems likely, therefore, that, as with CLP, the existence of an affected relative (other than parent) does not appreciably increase the probability that a sibling will be affected.

2. One Parent with CP, No Affected Children. The probability that a person with cleft palate will have a child with cleft palate is estimated as 7 per cent by Fogh-Andersen,[13] though again the numbers involved are rather small (five out of 70).

3. One Parent and One Child with CP. Fogh-Andersen[13] found that out of 24 siblings of children with CP with one parent similarly affected, four, or 17 per cent, also had cleft palates. Because of the small numbers involved, this estimate is a rough one, but is the best available, to date.

As an aid to memorization, these figures may be rounded off and

given in the form of questions as encountered by the counsellor. Figures will usually be given for CLP only, since the values for CP are essentially similar. When using these risk rates, it must be kept in mind that they are averages, and that the true risk for a particular case may differ widely from the given figures.

1. Q. *My husband (wife) and I are unaffected, and we have a child with CLP. What is the chance of having another child with CLP?*
   A. About 5 per cent for each of your children.
2. Q. *My husband (wife) and I are unaffected, and we have had two children with CLP. What is the probability of having still another affected child?*
   A. About 10 per cent. (Data inadequate for CP.)
3. Q. *My husband (wife) has a CLP, and we have no (or all normal) children. What is the chance that we'll have an affected baby?*
   A. About 5 per cent for each of your children.
4. Q. *My husband (wife) has a CLP, and we have a child with CLP. What is the chance of having another affected child?*
   A. Between 10 and 15 per cent for each of your children.

CLUBFOOT

As with many other common congenital defects, the counselling situation in cases of clubfoot is complicated by the fact that there are undoubtedly a number of ætiologically different types grouped in the same clinical category. Certainly the ones secondary to a spina bifida must be an ætiologically separate group (which may itself be heterogeneous), and there is some evidence to suggest that the type associated with dislocation of the hips may represent a separate category.[14] Böök's demonstration of an increased frequency of clubfoot in the siblings of patients with clubfoot when the parents are related is further evidence of genetic heterogeneity within the category of clubfoot.

The frequency of clubfoot has been estimated as about 1 per 1000 births,[47] but there may be wide differences between races.[53] Usually no simple pattern of inheritance is apparent. A number of German workers (cited by Böök,[5] and Neel[36]) have estimated the frequency of clubfoot in the siblings of patients with clubfoot as 2 to 3 per cent. In the author's rather small series of 77 cases (excluding those associated with spina bifida aperta or dislocated hips) with unaffected parents, the frequency of recurrence of clubfoot in the siblings is estimated as between 1.6 and 3.4 per cent. A value of 3 per cent would therefore seem suitable for counselling. It is interesting that in the author's small series this value does not appear to be increased in families in which there is an affected relative other than parent or sibling. Unfortunately, no reliable data are available as to the probability that the children of a parent with clubfoot will be similarly affected. However, Böök[5] suggests that the frequency of recurrence in siblings is distinctly elevated

(25 per cent or less) in families in which the parents are blood relatives.

The counselling risks for clubfoot may thus be summarized as follows, keeping in mind that the figures given will be appropriate for most of the cases encountered, but that a few cases, so far clinically indistinguishable from the others, will have recurrence risks widely different from those stated:

1. When the parents are normal and unrelated, and have a child with clubfoot (without spina bifida aperta or dislocated hips), the risk is about 3 *per cent* that any other child of theirs will be similarly affected.

2. When the parents are normal, but related, and have a child with clubfoot (without spina bifida or dislocated hips), the risk is between 3 and 25 per cent that any other child of theirs will be similarly affected.

CONGENITAL HEART DISEASE

We will exclude from our discussion of counselling those cases of congenital heart disease associated with some specific condition such as Mongolism, Marfan's syndrome, chondrodystrophia calcificans congenita, the Ellis-van Creveld syndrome or the maternal-rubella (Gregg) syndrome, since the risk of recurrence of the cardiac malformation will depend on the risk of recurrence of the associated disease.

A number of workers*, [26, 30, 44] have estimated the frequency of congenital heart disease in the siblings of patients with cardiac malformations, the parents being unaffected. The estimates range from 1.4 to 1.8 per cent, a remarkably good correspondence. However, since "congenital heart disease" is such a heterogeneous category, it would be useful to have a separate estimate for each type of malformation. Some types are so rare that suitable data are not yet available. By combining the results of several series, the author has derived estimates for the frequency of cardiac malformations in the siblings of patients with various types of congenital heart disease (Table 21). It should be noted that the figures have not been entirely corrected for the bias due to the method of ascertainment,[48] and so the given figures will tend to be underestimates of the correct values for counselling, but the error involved will be relatively small.

Thus it would seem that 1 to 3 per cent is a suitable risk figure to use for the specific types of malformation listed in Table 20 when counselling parents of an affected child about the possibility of a cardiac malformation occurring in a subsequent child. There is a need for similar data on other types of congenital heart disease. On the small

* F. C. Fraser: Unpublished observations.

TABLE 21. *Frequencies of Cardiac Malformations in the Siblings of Patients with Various Types of Congenital Heart Disease*

TYPE OF MALFORMATION IN PATIENT	NUMBER OF SIBLINGS	PERCENTAGE OF SIBS WITH CARDIAC MALFORMATIONS
Coarctation of aorta	104	1.9*,26,30
Interatrial septal defect	185	1.1*,26
Interventricular septal defect	324	0.3*,26
Patent ductus arteriosus	657	1.4*,2,26,30
Pulmonary valvular stenosis	187	2.1*,26,30,44
Tetralogy of Fallot	819	1.5*,26,44
All types	3412	1.5*,26,30,44

* F. C. Fraser: Unpublished observations

body of data available we suspect, for instance, that the recurrence rate for transposition of the great vessels may be higher than 2 per cent, and there is some evidence[25] that the recurrence rate for primary endocardial fibro-elastosis may approach 25 per cent.

In summary, parents who have a child with a congenital cardiac malformation may be advised that the average probability that a subsequent child will have a cardiac malformation is about 2 per cent, keeping in mind that for certain types of malformations and in certain families the actual probability may differ widely from this value.

DIABETES MELLITUS

In spite of the apparently universal agreement that there is a strong hereditary tendency in diabetes mellitus, there seems to be wide disagreement as to the kind of genetic mechanisms involved. Evidence has been put forward to support the theory that the disease is due to a dominant gene with reduced penetrance,[28] a recessive gene with external activating factors,[3, 20, 49] a recessive gene with full manifestation, provided the homozygous person lives to the age of 90,[43] or a gene pair that causes the adult type of diabetes in the heterozygous state and the juvenile type when homozygous.[21, 60] Even a sex-linked tendency has been invoked,[42] though this may be a statistical artifact.[35, 57] Occasional families seem to show dominant inheritance with a fairly high degree of penetrance.[7] This confused state of affairs makes genetic counselling difficult, to say the least.

Steinberg,[50] assuming simple recessive inheritance, presents tables giving the probability of a person's being genetically predisposed (homozygous, dd) for different degrees of relationship to a diabetic person, but goes on to say that there is at present no method of predicting whether or when a person who is genetically liable to diabetes will become diabetic. This is unfortunate for the pædiatric counsellor,

since the parents are likely to be worried about their children having diabetes early in life, and are not likely to think of limiting their family because of the possibility that their child would become diabetic at, say, the age of 60. Possibly the situation will be clarified when better methods for detecting genetically predisposed persons have been worked out, and it will be interesting to see how the use of cortisone to bring out abnormalities in the glucose tolerance test works out in this respect.[12]

One of the most widely quoted studies on the inheritance of diabetes is that of Pincus and White,[43] who concluded that their data on familial distribution of the disease would fit the expectations for simple Mendelian recessive inheritance *provided the persons at risk lived to the age of 90*. Unfortunately, the conclusions are often quoted without the proviso, and the parents of a diabetic child are told that their next child has 1 chance in 4 of also being a diabetic. This may be so (though there is yet no satisfactory evidence that it is) if the child lives to be 90, but the parents are liable to interpret this conclusion in terms of a 1-in-4 chance that the child will be a juvenile diabetic, and thus take an over-pessimistic view of the situation. The frequencies of diabetes actually found in the siblings of diabetics, both parents being non-diabetic, are much lower than 1 in 4. Thus Harris[21] found a frequency of 4 per cent, Steinberg and Wilder 5 per cent[49] and Watson and Thompson 8 per cent.[60] Bartels,[3] among the siblings of juvenile diabetics, found that 12 per cent were diabetic. These figures might be expected to rise as the siblings grow older.

Perhaps the most useful figures are those of Grunnet,[19] who presents the frequency of diabetes in the siblings of diabetics for various age groups. He divided his index cases into mild and severe ones and found that among the siblings of severe cases (parents normal), the frequency of diabetes in persons under 20 years of age was about 5 per cent, rising to 11 per cent by age 60. For the mild cases, the frequency of diabetes in the siblings was negligible until age 40 and again rose to 11 per cent by age 60. This corresponds rather well with the estimate of Reed,[47] based on the data of Harris,[21] that the sibling of a diabetic has a 12.5 per cent chance of becoming a diabetic by the age of 70.

Another question often put to the counsellor concerns the prospects for the child of a diabetic. Watson and Thompson[60] found that in the offspring of a diabetic patient and a non-diabetic spouse, about 2 per cent of the children had diabetes, but if the unaffected spouse had a family history of diabetes, this value rose to about 7 per cent (uncorrected for age). Reed[47] quotes a value of 13.7 per cent for the offspring of a diabetic parent, counting only offspring who had reached the age of onset of the parental diabetes. Grunnet's[19] estimate is intermediate, being about 7 per cent in those offspring who had reached

the age of 30 years. Ditzel[10] *et al.* report an interesting body of data on 100 children (three to 20 years old) of diabetic mothers. Fifteen per cent of them had a diabetic type of glucose tolerance curve. However, of nine with abnormal curves who were re-examined two years later, one had reverted to a normal curve, and two had become borderline. Probably a better value to use for counselling is the frequency of clinical diabetes, which was 9 per cent in the children of diabetic mothers[10] and in a similar group of children with diabetic fathers.[61]

Keeping in mind the many unknown variables in the situation, the pædiatrician may wish to use, cautiously, the following approximations as rough guides when advising parents about the familial distribution of diabetes mellitus:

1. The prevalence of diabetes mellitus in the general population is something over 1 per cent.[47] The cumulative incidence, i.e., the risk that each person runs of diabetes developing before age 80, is of the order of 6 per cent.[10]

2. When both parents are non-diabetic and they have a diabetic child, a subsequent child has roughly a 5 per cent chance of becoming diabetic before 20 years of age and about a 10 per cent chance of becoming diabetic by age 60.

3. In the case of a diabetic parent with a non-diabetic spouse, the probability that a child of theirs will become diabetic before age 30 is roughly between 5 and 15 per cent.

EPILEPSY

There have been a number of extensive studies on the familial distribution of epilepsy, but the task of extracting risk rates suitable for genetic counselling from them is a difficult one. The difficulties arise from differences between studies in the method used to select propositi, in the criteria used to diagnose epilepsy in the relatives, and in the amount of effort expended in investigating families.

By far the largest study is that of Lennox,[27] who selected propositi apparently by the fact that they had gone to a neurologist or neurological clinic because of epileptic seizures. He found that 3.2 per cent of the parents, sibs and children of epileptic patients were themselves epileptic, the proportion being about the same in these three groups of relatives. (The problem of how many seizures were required to classify a relative as epileptic was settled by compromise—in half the relatives one seizure, and in the other half two seizures was accepted.) The propositi were classified as "essential," without known antecedent brain pathology, and "symptomatic," with antecedent gross brain lesions. In the "essential" group the frequency of epileptic relatives was 3.6 per cent as compared to 1.8 per cent in the relatives of

the "symptomatic" group. The frequency of affected relatives was highest (7.6 per cent) in the group with "essential" epilepsy appearing in infancy. All these values are significantly higher than the 0.5 per cent level (based on the U.S. Army draft) used by Lennox as a rough estimate of the frequency in the general population. Similar findings were reported by Harvald.[23] Alström,[1] in a study of Swedish Neurology Clinic patients, obtained slightly lower figures—1.5 per cent for the sibs and 3.0 per cent for the children of epileptic propositi, and concluded that this was no higher than the rate in the general population. Perhaps the most promising approach is that of Ounsted,[38] who grouped his propositi and their affected siblings into eight clinical categories of seizure, and was able to show that the pattern of seizures in siblings was characteristic for each group of propositi. For instance, when the propositus had febrile convulsions, 17 per cent of the sibs also had febrile convulsions, but only 4 per cent became "chronic" epileptics. When the propositus had epilepsy, resistant to treatment and persisting, about 10 per cent of the sibs had febrile convulsions and about 7 per cent became "chronic" epileptics. More investigations are needed along these lines.

Finally, the results of the Metrakoses[32, 33] are noteworthy. They studied the families of propositi with "centrencephalic" epilepsy in the pædiatric age group, who had a history of recurrent seizures, no obvious neuropathology, and a centrencephalic electroencephalographic pattern. Among the siblings of the epileptic propositi, 22 per cent had a history of one or more seizures, as compared to 4 per cent in the siblings of control propositi. However, about half of the 22 per cent of affected siblings had only one or two seizures over a short period of time. Of the other 11 per cent, about half had several convulsive episodes and constituted a definite medical problem to the family, but recovered. The other 5.5 per cent became "chronic" epileptics. It is this group that should form the basis of a counselling risk rate, since these are the children that put a serious burden on the parents.

In conclusion, it can be stated that the clinical category of "epilepsy" represents a heterogeneous mass of diseases, with varying degrees of heritability. Convulsions may appear as a symptom of a number of rare diseases showing clear-cut Mendelian inheritance, such as amaurotic idiocy, epiloia, phenylketonuria and sickle-cell anæmia. Excluding these, the parents of a child with epilepsy may be told that: (*a*) If the epilepsy is "centrencephalic" ("idiopathic," "essential"), the risk of a sibling's becoming a "chronic" epileptic is about 5 per cent. (*b*) If the epilepsy is "symptomatic," the risk of a sibling's being a "chronic" epileptic is low, probably not much larger than that in the general population. (*c*) No reliable data are available to estimate the risk that a person who has epilepsy in childhood will have epileptic children,

but it is reasonable to suppose that the average risks will be no higher than the foregoing figures.

The counsellor may also be asked about the possibility that an adult with epilepsy will have epileptic children. If the parent's seizures are "idiopathic," the average risk of a child's being epileptic appears to be about 3 per cent[1, 27] for each child. If the parent's seizures are "symptomatic" in origin, the risk for the children will be somewhat less than this. Unfortunately, the electroencephalogram appears to be an unreliable indicator of a genetic predisposition to seizures, and is of little use in guiding the genetic counsellor.[33, 38]

FIBROCYSTIC DISEASE OF THE PANCREAS

The frequency of fibrocystic disease of the pancreas in the siblings of affected children is compatible with the expectation for simple Mendelian recessive inheritance—i.e., 25 per cent.[4, 9, 29, 51] It may be possible in some cases to detect the heterozygous carriers of the gene by abnormalities in their sweat electrolytes, but so far there is no consistent method of detecting heterozygotes. It is interesting to speculate as to why the disease appears to be so common, in spite of the strong selection pressure against the mutant genes, whether several loci or a series of multiple alleles are involved, and what genotypes are responsible for the "partial" forms of the disease. In any case, the parents of a child with fibrocystic disease of the pancreas may expect that any subsequent child of theirs has 1 chance in 4 of being similarly affected.

MENTAL DEFICIENCY

Mental retardation is another highly heterogeneous category containing many ætiologic types, differing widely in their degree of heritability. There are a number of clinically distinguishable, rare, simply inherited diseases producing mental deficiency, such as anhydrotic ectodermal dysplasia, epiloia, galactosæmia, gargoylism, Laurence-Moon-Biedl-Bardet syndrome, and phenylketonuria.[15] Other specific types of mental retardation, such as cretinism, Mongolism and kernicterus, are less clear-cut, genetically. In addition, there is a large group of "non-specific" mental deficiencies in which no specific clinical feature is distinguishable. Penrose[40] states that for a child with severe, non-specific mental deficiency (imbecile or idiot), the risk that a sibling will be similarly affected is about 3 per cent. This would seem a suitable figure for counselling in such cases, always keeping in mind that the actual risk for any particular case may be much higher or much lower than 3 per cent.

MONGOLISM

Much has been written, but little is known, of the cause of this syndrome, about which the pædiatrician is often queried concerning the possibility of recurrence in subsequent children. According to Penrose,[40] if a mother has had a child with mongolism, her risk of having another is two to three times as high as that of other women in her age group. Thus any woman 25 years of age has about 1 chance in 2000 that her baby will be a mongoloid defective,[37] but if she has already had such a child her risk of having another is about 1/800. At the age of 45 any woman has about 1 chance in 40 that her baby will be a mongoloid defective, but if she has already had one, her risk will be 1/16.

RHEUMATIC FEVER

The familial nature of rheumatic fever has been recognized for a long time, but how much of the familial distribution is the result of a genetic predisposition and how much is due to familial environmental factors is still not entirely clear. The causal rôle of certain environmental factors seems well established, and there are now several studies that demonstrate a genetic basis underlying the "rheumatic" response to beta-hæmolytic streptococcal infection.[52, 58, 62, 63] However, there is disagreement as to the mode of inheritance of the rheumatic predisposition. Wilson *et al.*[63] claim simple recessive inheritance with full penetrance by the end of the age range at risk, but Uchida[58] and Stevenson[52] think that the data are not compatible with any such simple interpretation.

For counselling purposes the risk for a sibling of a child with rheumatic fever having the disease will vary, not only according to the child's genetic constitution, but also according to the environment, and it must be remembered that *published frequencies of affected siblings are valid only for the particular age groups, races, climates and cultures studied.*

Thus Wilson *et al.*,[62] studying the families of patients in a cardiac clinic in New York City, report that the frequency of rheumatic fever in the siblings of patients with rheumatic fever (both parents being unaffected) was 22 per cent, whereas Uchida,[58] using white cardiac clinic patients of low income groups in Toronto, reported a figure of 8 per cent, and Stevenson,[52] attempting a complete survey of cases in Northern Ireland, also reported a frequency of 8 per cent. All these figures would be expected to rise as the children at risk grew older, and Stevenson[52] has demonstrated this by following up his original group of families, four to five years later. The sibling frequency rose, in the

group with unaffected parents, over this period from 8 to 11 per cent.

For siblings of patients with rheumatic fever when one parent had also been affected, the frequency of rheumatic fever was about 19 per cent in Northern Ireland[52] and about 43 per cent in New York City.[62]

Thus it seems that risk rates for counselling can be stated only within rather wide limits. It is probably safe to say that, *in temperate climates and lower income groups, if a child has rheumatic fever, the probability that a subsequent sibling will also have rheumatic fever lies between 10 and 25 per cent if both parents are unaffected, and between 15 and 50 per cent if one parent is affected.*

Even if the lower limits are the correct estimates, it would seem that siblings of children with rheumatic fever are much more susceptible to rheumatic fever than are members of the general population, and should be treated accordingly. This might be expected to cause a decided decrease in the risk rates for siblings of patients with rheumatic fever.

CONCLUSION

The reader may have gathered by now that the figures available for genetic counselling in the commoner pædiatric diseases are not as reliable as they might be. Much new information is needed. More specific ætiological entities, for which precise estimates of probability of recurrence in relatives can be made, need to be separated out of heterogeneous clinical categories. New means of detecting genetic "carriers" of disease will greatly increase the precision of the counsellor's predictions in many cases. In the meantime the pædiatrician consulted about the possibility of familial occurrence of a disease must make the best of what information is already available. The present article has attempted to state the appropriate risk rates for various counselling situations, and to point out the shortcomings involved in the establishment of these figures, so that proper caution will be exercised in applying average risk rates to individual situations.

SUMMARY

Estimates are given of the probability of occurrence in siblings and other relatives of children with anencephaly and/or spina bifida aperata, cleft lip and/or palate, clubfoot, congenital heart disease, diabetes mellitus, epilepsy, fibrocystic disease of the pancreas, mental deficiency, Mongolism and rheumatic fever. The need for caution in applying these figures to individual cases is emphasized.

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SCHIZOPHRENIA IN CHILDHOOD

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It is the feeling of this writer that the most useful purpose this paper can serve is to present a general picture of the present understanding of childhood schizophrenia. The suggestion[18] that the term "childhood" should refer to the first 12 years of life has been followed, since schizophrenia having its onset after 12 years of age follows the pattern of the adult disorder. A more complete bibliography can be found in Goldfarb's recent book, *An Annotated Bibliography of Childhood Schizophrenia*,[43] which covers all contributions made up to the end of 1954. Such factors as heredity, some aspects of constitution, and the relevance of changes in the electro-encephalogram are not discussed.

THE HISTORICAL PERSPECTIVE

Twenty-five to 30 years ago the problem to be considered would have been whether or not schizophrenia existed in pre-puberal children. At that time the criteria for diagnosis were those applied to schizophrenia in adults, but there had been sporadic papers and discussions in books on the subject of psychosis, madness or insanity in children long before. Perhaps the earliest would be the report by Benjamin Rush[81] on four cases of pre-puberal madness seen by him between 1799 and 1808. Between 1870 and 1900 more than 20 reports[43] appeared on psychosis in children. The earliest paper published on this continent in which there was specific description defining schizophrenia in childhood was that by Howard Potter[75] in 1933. Brill,[20] Kasanin[59] and Potter[75] were largely responsible for calling attention to the occurrence of psychosis in childhood, while at a later date Despert[22-29] and Bradley[19] clarified and elaborated the clinical picture of schizophrenia in children, stressing the differences between the condition in children and that in adults.

During the decade following 1940 there was established the unique dynamic identity of schizophrenia as an illness of childhood, with differential descriptions of these children establishing categories of disturbance within the illness. The greatest impetus to this development came from the writings of Bender[7-13] and Kanner[51-56] and later from those of Mahler,[63, 64] Putnam[76, 77] and Rank.[79]

The present decade has been a period of increasing recognition that we are not dealing with a separate entity, but rather with a group of related and overlapping clinical syndromes in which the child shows a certain pattern of symptoms arising

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from a regression in, or an arrest of, ego development. This trend has lent increasing importance to an understanding of the nature of the infantile ego, especially of those factors concerned with its establishment and development.[46, 47, 78]

THE EGO

The functions which comprise the ego are not evident in the newborn child, but are subject to development from early undifferentiated psychic states. This development is a combination of processes of maturation of the inborn apparatus and processes of learning related to the ongoing experience by the infant of the total environment. A complete listing of these functions is extremely difficult at present, partly because they have a great degree of interdependence and interrelationship. The following functions have been suggested by Beres:[17] (1) the relation to reality: the child's ability to differentiate between internal reality (phantasy) and external reality; (2) regulation and control of instinctual drives; (3) development of object relationships; (4) thought processes; (5) the ability to use the more mature defense functions such as repression, rather than the more immature such as denial and turning instinctual drives back upon the self; (6) autonomous functions such as perception, language, memory and motility, each of which has its own development pattern; (7) synthetic functions: the organizing ability of the psyche having as its tools the other ego functions.

In childhood schizophrenia we are concerned primarily with a disturbance which manifests itself in every area of function and development of the ego. Disturbances largely limited to one or two areas of ego functioning are found in character disorders and other less severe behaviour disorders.

THE CHILD

Childhood schizophrenia is the end-result of a global disturbance of ego functioning having multiple ætiological determinants. It varies in severity of clinical symptomatology as the ego disturbance varies on the continuum from more to less severe. Each of the following descriptions of the child represents not only some part of this continuum of disturbance, but also that facet of schizophrenia studied by the particular worker concerned.

Childhood Schizophrenia

Bender[7] has a consistent, biologically oriented theoretical framework and summarizes the problems of the child in the following terms:

> The emotional problems of the young schizophrenic child are related directly to anxiety of biological origin; to the primary disturbance in homeostatic control of body functions, in respiratory patterns, and in speech and language development; to the primitive and inadequate tonic responses to perceptions of all kinds and primarily

to gravity, space and objects; and to the tonic-neck-reflex dominance of impulses and activity. Secondary symptom formation may result in withdrawal, autism, or regression in some cases; or in panic states, temper tantrums and neurotic phobias, fears and compulsions in others. Or both responses may be present coincidentally or alternately in the same child. If, and as, ideation phantasy and some capacity to be articulate develops, the child may express his profound difficulties in personal identity, body imagery, body boundaries, or orientation in space and time, and object relationships.

Disturbances in vegetative function give rise to excess lability of the vaso-motor system; unpredictable reactions to illness; loss of patterning of sleeping, eating and elimination habits; precocious or delayed puberty and growth discrepancies.

Disturbances in motility are apparent as unevenness in motor development, awkwardness and poor control of gross movements. There is excess anxiety around developing new motor patterns, and early reflex pattern activities may persist from early infancy and continue in the older child as mannerisms or stereotyped play activities. An example of the last is the persistence of the "choreo-athetotic" hand activities normal in the first year of life into later years and often their incorporation into the handling and tapping of small objects. Characteristic is the tendency of the schizophrenic child to try to "melt into" an adult when child and adult are in physical contact.

The simultaneous presence of early and late patterns of maturation, of retarded and precocious behaviour, is particularly seen in the perceptual and language spheres. Examples of these would be the use of vortical movements in drawings at a more mature level or the use of the third person pronoun when referring to the self. If the onset of the disorder is before language is well established, there is mutism, which may be partially overcome with return of distorted speech: or speech may deteriorate to a fragmentary form. Or there may be a precocious use of speech in a child who otherwise appears retarded.

The pattern of the disturbance shows differences depending on the age of onset. Bender's[8] description of the child having onset of schizophrenia during the first two years of life approaches Kanner's[54] description of the older child with early infantile autism. With the more common onset between three and five years of age, regression may be insidious or abrupt with loss of acquired patterns of behaviour associated with severe anxiety and a marked, clinging dependence on the mother. Anxiety may disappear with the onset of a complete regression, and there follows a slow gain of some patterned behaviour distorted by the schizophrenic process.

Early Infantile Autism

Kanner[51, 56] emphasizes the severe disturbance of the capacity for human contact in the group of children whom he designated as showing early infantile autism.

These autistic children manifest a profound withdrawal from contact with people, dating from the second half of the first year of life with a skilful and even affectionate relationship to objects. The obsessive desire for the preservation of sameness of the environment leads to severe tantrums or panic if, for example, the arrangement of furniture in a familiar room is changed. They have intelligent, pensive faces despite the extremely low level of intellectual functioning. There is either mutism or the kind of language not intended for interpersonal communication. This language shows a peculiar reversal of pronouns, neologisms and metaphors. As infants they are frequently diagnosed first as deaf, and later as mental defectives. They may, however, show decided, unemotional, self-contained intellectual achievements.

Bergman and Escalona[14] described a group of young, severely disturbed children who show unusual sensitivity to sensory stimulation evident in the first 18 months of life. They are also excessively vulnerable to emotional hurt. There is some resemblance to Kanner's early infantile autism except that they do not show language peculiarity and the extreme absence of human relationships.

Autistic and Symbiotic Psychosis

Mahler[63, 64] greatly increased our understanding of the differences between the syndromes described by Bender and by Kanner when she differentiated between autistic psychosis and that which she designated as symbiotic psychosis.

When the mother is never perceived emotionally and remains a "part object" without special interest to the infant, being to him like an inanimate object, the *autistic psychosis* occurs. When the infant has taken the next step and perceived the mother as if part of himself (the symbiotic state), but has not progressed to demarcating his own body image, separating self and non-self, the *symbiotic psychosis* occurs. So long as the child can maintain this illusion of psychic fusion with mother, there is no flagrant disturbance. But in the third or fourth year of life ego differentiation and psycho-sexual development challenge the child with a measure of independence from the mother. With this threat of "loss" of mother there is felt to be a "loss" of part of the self, and there begins a process of ego fragmentation associated with panic reactions.

After the overt psychotic process has been initiated in the form of an autistic or symbiotic state, the clinical manifestations may change and the autistic child increasingly show symbiotic features or the symbiotic child increasingly show autistic features.

Shugart[84] has described the differences between the autistic and

symbiotic child in each of the five main areas in which are seen manifestations of ego functions. These areas are orientation to people, to reality, and to play; the use of motility and sensory modes; and speech.

The autistic infant is oblivious of people, but, when older, may approach them to demand satisfaction of some want. The symbiotic child clings to his mother, struggles against separation from her, panics at her absence, yet provokes her by teasing behaviour when she is present. He manifests extremes of love and hate. When with other children, he may watch them play or show sporadic parallel play.

The autistic child is indifferent to most objects, and his strong attachment to specific objects fails to result in learning. His interests are restricted to a narrow range, particularly those things that spin or turn, knobs, switches and small fragments of objects. Any use of objects is perverted or bizarre. The symbiotic child's contact with objects suffers from disturbance in quality and not quantity. He shows a special interest in anything he senses as threatening his bond with his mother. In spite of the appearance of greater contact, it is often said of him, "He doesn't seem to be learning as he should," or, "He'll learn only what he is interested in." The symbiotic child learns and masters situations in a distinctive manner. He rejects trial and error and is "a watcher" of the performance of others. Several weeks later he may produce the same performance completely mastered. However, having performed something once, he may refuse to demonstrate his acquired skill again. Alternatively, he may acquire a skill while no-one is looking and performs it only when he thinks himself unobserved. This type of mastery is manifested in learning to control the bowels, to speak and to walk, as well as in other ways.

The autistic child shows no "playfulness," and games such as "pat-a-cake" and "peek-a-boo" are particularly noted to be absent. Toys are ignored or destroyed. The symbiotic child does not destroy toys, and engages in brief, clumsy play. Most characteristic is an early interest in his mother's domestic activities and the mechanical household equipment.

The autistic child is fearless, adept at climbing, and often precocious in development of motility patterns. The symbiotic child is fearful of high places and has poor muscular co-ordination.

The autistic child frequently mouths and fingers objects. The symbiotic child is often more preoccupied with smelling objects or the taste or feel of certain textures.

Most often the autistic child has some words at one year of age with later muteness. The symbiotic child retains his speech in many cases, but the accretion of new vocabulary is slow, and speech is used for his own private purpose or to communicate wants.

Atypical Children

These children are described by Rank and her co-workers[76, 79] as showing "marked personality deviations which might be variously described as infantile dementia, psychosis, autistic disturbance, pseudo-retardation, or arrested development due to emotional factors."

The diagnostic features are noted by Hirschberg and Bryant[48] to be those that are essential elements in any of the various categories of childhood schizophrenia.

There is a lack of uniformity in and integration of ego development with some well-developed ego functions existing alongside arrested and regressed ones.

Impairment in the sense of identity and the sense of reality is associated with impaired perceptions of the physical world and impaired integration of these perceptions into a total whole. Such children show a tendency to withdraw from reality with an increased intensity of phantasy. Eventually there is an intrusion of phantasy into reality that may be of such degree as to amount to a loss of contact with reality.

Impaired communication with and relationship to others frequently manifest themselves as difficulties in verbal communication and in withdrawal from people.

"Borderline" Schizophrenia

There is another group of children, described by Ekstein and Wallerstein,[30, 31] who are usually referred to as "borderline psychotic" whose ego functioning may shift rapidly and abruptly from adequate adjustment to external reality, to complete distortion of this reality by inner phantasy. This shift occurs without adequate conscious control and with minimal reality or internal determinants for it. Conversation and play suited to the age of the child may be interrupted by a sudden crumbling of neurotic defences and intrusion of phantasy into reality. During this psychotic phase he may resemble the autistic, the symbiotic or the unusually sensitive child described by Bergman and Escalona.[14] The change back is equally rapid, the break with reality lasting for minutes or an hour or more.

Other children belonging in this group have been called severe behaviour disorders, psychotic, schizophrenic, or children of deviant development. They belong here because of showing either sudden or temporary shifts in ego function or because of disturbances of total ego functioning short of the severity found, for instance, in the children of atypical development described by Rank and her co-workers.

Geleerd[37, 39] has described some of the traits of this type of child. Although their overt behaviour suggested a diagnosis of behaviour disorder, they showed deviant ego function in many areas, and some

became obviously schizophrenic during adolescence. In any group situation they became uncontrollably aggressive or completely withdrawn. But when alone with an adult, they showed extremely pleasant, adequate behaviour. During tantrums they were often dangerously paranoid and out of contact with reality and became more paranoid with firm handling. In this situation they responded only to the loving, soothing attitude of a familiar adult. They showed extreme interest in animals associated with great sadism, and often also excess interest in such things as cars, trains, sewers and pipes. In their past history they revealed deviations, often considerable, in phases of ego development.

Weil[90, 91] has pointed out that the neurotic child does not have marked ego disturbances. Nor does he alternate within weeks from one type of symptom to an entirely different one. She describes a series of patients whom she considers schizophrenic, who are either extremely passive or phobic and obsessive. Their histories revealed multiple deviations in ego functioning, including acceleration of development of isolated areas and under- or over-intensity of expression of emotions and impulses, apparent from an early age. Early, too, were multiple anxiety manifestations which were intense and long lasting. Particularly apparent was the failure of this type of child to enter latency, during which period sexuality should be minimally apparent and aggressive impulses much mitigated. As Anna Freud[35] said: "During latency the ego assumes superiority, directs the activities of the child, establishes the reality principle and effects the first real adaptations to the external world." These children showed unmitigated outbursts of love and hate in close alternation during latency.

Special Studies

Arising from consideration of childhood schizophrenia from the standpoint of ego functioning, there has been an increased interest in investigation and evaluation of developmental disturbances of the autonomous ego functions and a renewed interest in the work of Piaget[73, 74] and Werner.[92]

Norman[67] has studied the manner in which schizophrenic children build up knowledge of the world and themselves. She showed how preoccupied they are with geometrical forms and colour, with special attention to small details. Missing is a concern with function and use of an object, with all that is related affectively to it. Thus objects are a series of details, a collection of perceptual properties rather than functioning wholes. This suggested failure of generalization and a concrete rather than a conceptual way of thinking.[82] There is a tendency to attempt to retain and often reinstate particular experiences, but with a failure to modify them in any way to link them with the

child's own need and activities. This last is seen especially in what Despert[23] has described as the dissociation between language sign (mechanical and repetitious use) and language function (use for communication). Affective experience links more closely with experience of outside objects, and such objects have the qualities of the affect. For instance, they may be seen as hating, destructive objects.

In a later paper Norman[68] reported on a similar study on withdrawal and affect manifestations in schizophrenic children. She observed little actual physical avoidance, whereas looking at people "out of the corner of the eye" was prominent as an active visual avoidance which showed a significant association with the presence of mutism. She also noted an occasional active auditory avoidance which is readily confused with deafness.

Affective failure was illustrated by the children who would give a verbal description together with a flat, emotionless, melodramatic play-acting of the feeling of the moment. Opposite feelings were expressed together or in sequence, each affective discharge appearing in typical all-or-none fashion. Affective response might also be after a long delay or be substituted in part by "choreo-athetoid" types of movements.

There have also been a number of studies on speech and language. Kanner[63] analysed the language of children with early infantile autism. Goldfarb and others[42, 83] have commented on the lack of desire for communication, the preference for singing over speech, and the deviations of intonation pattern with dissociation of intonation from meaning. For instance, a statement may be made with the intonation of a question.

EARLY RECOGNITION

This demands the early recognition of deviant ego development. Weil[90] has mentioned some of the evidence which might be found in infants. Some show deviant drive endowment, being either sleepy and apathetic or sleepless and restless. Deviant patterning of development is indicated in those infants who are hypertonic, show excess crying in spite of yielding care, have persistently erratic patterns of eating and sleeping, and constantly have regurgitation and vomiting or diarrhœa without detectable cause. A little later in life are seen the disturbances in maturational sequences such as the beginning of walking without a previous period of standing or a sequence of talking-muteness-talking. Another early sign is tension, manifested in extremes of auto-erotic or auto-aggressive behaviour such as long periods of rocking, head banging and hair pulling. These children may falter at each developmental step, such as the change to solid food or from standing to walking, for a long time.

The failure of development of adequate object relationships in the infant is indicated by such things as failure to smile at the mother's face, no anticipatory gesture before being picked up, failure to hold on when carried, no response to cuddling, and lack of touch exploration of mother's face and body.

There is also the absence of normal transitory disturbances of early childhood. Between seven and 12 months of age there should be "stranger anxiety" indicating the beginning of individuation and differentiation by the infant. Between one and two years of age there are normally some sleep disturbances indicating that the child is experiencing some of the tensions of beginning to separate from his mother.

The important feature is the co-existence of some disturbance in every area mentioned: it is the total picture rather than the single symptom. With this in mind, disturbances in the formation of object relationships and in sleep patterns should give rise to most concern.

Patient Examples

The examples which follow illustrate the over-all picture presented by some of these children.

CASE I. Jimmy had a happy start in life and enjoyed being over-indulged with bottle feeding until 2 years of age. When the bottle was taken from him, he had more than the usual number of tantrums for a month, and suffered severe sleep disturbance. His parents were not unduly concerned, since he seemed well adjusted in every other respect.

At the age of 2½ he had his tonsils removed and on his return home found his mother in a moderately severe depression. Three weeks after this he progressively gave up speech and became increasingly bizarre in his behaviour and preoccupied with music. At the age of 3 years he would spend much time sitting and staring into space or walking up and down and crying pitifully and agonizingly while seemingly oblivious of everyone. He did not care for children and shied away from adults. By this time he was completely mute. By the age of 5 he was described as constantly on the move, banging his head against objects and his fist against chairs, walls and the like, humming tunes for hours, and almost continuously tearing books and magazines.

CASE II. Carol had done a great deal of head banging and body rocking all her life, but particularly before 2½ years of age. Carol's mother had never been too much aware of what Carol was or was not doing. When Carol was 2½, her mother became aware of her clumsiness and poor co-ordination, and noticed that she was a great deal on her own and was preoccupied with the repetitious play of putting wooden blocks in and out of boxes. She was still not talking. Shortly after this, Carol began making efforts to talk and soon began producing an almost continual incoherent mutter in which no words could be distinguished. It was not until she was 4 that her mother noticed the first clear single words occurring at all frequently.

At the age of 5 years, on one occasion, Carol dropped a marble she was playing with, and became panic-stricken. She clasped her head in her hands and moaned, "My head, my head." For several days following this she was heard to mutter to herself, "Sew it up, sew it up," while making stitching motions around her neck. Around this time her speech still contained a large element of incoherent muttering, but much more could be understood, and she would say such things as "Why Indians wash—feed animals, feed babies—Carol big girl-baby—Cowboys fight—go to jail—fun in jail—

why Indians ride horses." These disjointed phrases would occur while she was playing with a collection of toy Indians and animals.

ÆTIOLOGY

It seems to be of increasing general acceptance that the ætiology of all childhood schizophrenia involves the interaction of various combinations of constitutional and psychological factors.

Bender[7] summarizes her concept of this interaction as follows: Schizophrenia is "a maturational lag at the embryonic level in all the areas which integrate biological and psychological behaviour; an embryonic primitivity or plasticity characterizes the pattern of behaviour disturbance in all areas of personality functioning. It is determined before birth, and hereditary factors appear to be important. It may be precipitated by a psychological crisis, which may be birth itself, especially a traumatic birth." She felt that the best understanding of these problems of maturation in the schizophrenic infant came from Gesell's[43] analysis of the maturation of the fœtal infant.

The psychological factors of ætiological importance are disturbances within the early parent-child relationship. These may arise from the emotional disorganization of the child, his lack of "sending power," or may result from extreme emotional unavailability of the parents (particularly the mother) or from an inordinate need of the mother for symbiotic fusion with the child. Contributing factors are traumatic events such as an actual loss of a parent, illness in early life or organic brain syndromes in the child. It can be understood that some children become schizophrenic even with the best maternal care, and others tolerate extremely poor care without such a grave disturbance developing.

The quality of the maternal care is of greater importance than the quantity, and the pathological features can be discerned from consideration of the character structures commonly associated with parents of schizophrenic children.

The Parents

A wide range of character types has been described for parents of these children, in relation to both the various clinical groups and the findings of different workers in the field. These parents seem to range from the "normal" to the extreme of both parents being overtly psychotic.

Kanner[54] has described a consistent character disorder of parents of children with early infantile autism and has aptly referred to them as "refrigerator parents." Both parents nearly always have a high in-

telligence, and are successful in careers requiring minimal interpersonal relationships. They are serious, disdainful of frivolity, undemonstrative, cold and formal in all their relationships. Towards the child they are mechanical in detached attention to his material needs. They read all the books on child care and rigidly "stick to the rules."

Bender[8, 9] and her co-workers have concluded that the schizophrenic child does not come from a specific kind of home. They feel that much of the disturbance shown by parents is due to the impact of the child on them.

Rank[79] divides the mothers into two main groups. The first consists of those with diagnosed psychoses: schizophrenics with remissions and more frequently manic depressives who have had depressive episodes shortly after the birth of a child. The second is the predominant group and is made up of extremely immature women incapable of warm relationships, who on the surface give the impression of being well adjusted. The vitally important element of genuineness is lacking in their maternal feelings, depriving them of spontaneity and tenderness.

Mann[65] has described personality traits that he observed in a large group of parents of pre-school schizophrenic children. They showed a pervasive hostility in all their relationships, but intense denial and other techniques were used to manage and hide this. Their great hostility was remarkably disguised and under rigid control. When they were made aware of their hostility, there was panic followed by attempts at restitution through highly intellectual discussions. Loving feelings were frequently expressed, but were shallow and covered other unacceptable feelings. The profound sense of guilt manifested itself in a pathetic desire to impress others with their normality. There was a fear of closeness with people and yet an inability to separate themselves from them. The only rapport of husband and wife was in intellectual interests, and yet they stuck together tenaciously in a marital relationship under constant strain. When pregnant, the mothers could think of the fœtus as a girl with some sense of familiarity, but thinking of it as a boy conveyed a total feeling of strangeness and anxiety. The mother's anxious, domineering pressure made the fathers totally ineffective in the family situation, and the fathers themselves were passive, dependent and in fear of their wives. Their rage at feeling forced to assume the duties of a woman in the home remained unexpressed.

DIFFERENTIAL DIAGNOSIS

Shugart[84] considers disturbances in relationship capacity to be of central importance in the diagnosis of schizophrenia, but emphasizes that such disturbances must be associated with some pathology in all

other areas of functioning. These features, which reflect the total ego involvement, are not found in the other diagnostic groups with which schizophrenia may be confused.

Mental Deficiency

The difficulties in differentiating between schizophrenia and mental deficiency are increased by the not frequent occurrence of both conditions in the same child. In uncomplicated and fairly typical cases there is seldom any difficulty, since the mentally defective child makes a good emotional relationship consistent with his mental age. However, his simple and more infantile ways of relating may be mistaken for "autism," especially since he is often mute and shows some bizarre motilities. The difficulties begin when the mental deficiency is complicated by one or more of the following organic features: emotional disturbances, secondary to the mental defect and environmental stress; some degree of total ego deviation which may be minimal in degree or reach such proportions as to constitute childhood schizophrenia.

Many mental defectives have varying degrees of organic brain damage, and this may sufficiently disturb ego development as to produce a form of childhood schizophrenia. When of less degree, this may be the cause of bizarre and often primitive motility patterns: some fragmentation in the thought processes: marked perceptual disturbances: impulsivity of emotional expression. Of central importance is the maintenance of reality testing and relationship capacity consistent with the mental age of the oligophrenic child.

Bergman and his co-workers[16] give a good picture of the situation when they note that 15 per cent of those admitted to an institution for retarded children showed some form of schizophrenia. Other workers[61, 69, 70, 80] report similar findings. These schizophrenic cases may be divided into the following categories: (1) nuclear schizophrenia erroneously diagnosed; (2) oligophrenia with superimposed schizophrenic patterns (*Pfropfschizophrenia*), either with two co-existing endogenous defects, or with oligophrenia operating as any other organic defect—i.e., the child is less able to cope with his environment; (3) oligophrenia with unusual behaviour which is not clearly suggestive of schizophrenia.

These workers[61, 69, 70, 80] report that the pattern of psychological tests is of help in diagnosis. The oligophrenic, in contrast to the schizophrenic, shows deviations in intelligence tests results which are diffuse rather than around multiple foci, has higher performance rather than higher verbal levels, and improves with urging and praise rather than fails to improve. Other workers[4, 15, 21] have also reported on patterning of the test results.

Hearing and Speech Disorders

Since deaf children may also have "minimal brain damage" in addition to a handicap in establishing relationships, they may have isolated, withdrawn personalities. But a good relationship can eventually be established. They may also show evidence of deviant ego development, especially during the pre-school years, and often diagnosis has to wait on time to show the unwinding pattern of personality and the response to therapy. Occasionally an obvious schizophrenia will develop in a child known to be deaf. Diagnosis depends on a full and complete history of development of the disorder together with careful observation of the child over a period of time. It is assisted by repeated audiometric evaluations, although these are unreliable when the child has associated organic brain disorders or prominent disturbances in relationship capacity. What has been said of deafness applies also to word deafness[58] (verbal auditory agnosia). These latter children will respond to sounds, but not to words, and are usually mute, but may have sparing speech.

Organic Disorders

The problem of the relationship of schizophrenia to *Heller's disease*[49] (dementia infantilis) is a vexing one. Benda[6] wonders whether Heller's disease is specific enough to maintain as a separate morbid entity and follows the general thinking at present in considering it a neurogenic disorder of which it cannot be said whether the pathology is "post-infectious," degenerative or metabolic. It may well include some of the lipoidoses and the leucencephalitides.

The only lipoidosis which may cause trouble in differential diagnosis is *gargoylism*. This condition has a variability in rate of progress and succession of organ involvement, and mental symptoms may greatly predominate during the early stages.[6] These last may occur as the only manifestations of the disorder for many months, and are symptoms of retardation in the late infantile form and of psychosis in the pre-juvenile form.

Phenylpyruvic oligophrenia may occasionally present with behaviour patterns of psychosis rather than idiocy, the child showing only slow deterioration in intelligence.[6]

Familial dysautonomia more readily may be mistaken for schizophrenia.[32] There are prominent problems in emotional control, motility disturbances and defective physiological homeostasis reminiscent of schizophrenia. Absent are the disturbances of reality relationship and disturbed thought processes. There are typical somatic disturbances related to autonomic dysfunction.

The child with *diffuse brain damage*—"minimal brain damage"—

shows hyperactivity, distractibility, poor concentration, impulsivity and perceptual defects, but does not show disturbances in other areas of ego functioning. However, he may be so impulsive that his fleeting relationships go unnoticed, giving a false impression of a primary defect in relationship capacity. Fuller[36] has described a type of adjustment in such children closely simulating schizophrenia. Organically determined deviant perception and integration of reality, associated with emotional instability, lead to reactions that are peculiar. But the children have concealed capacities for relationships and especially differ in this respect from those with organic brain syndromes as an ætiological factor in their schizophrenia.

Neurosis

Ego function, especially in the area of reality testing, is little or not damaged in neurosis, but badly shattered in psychosis. Even bizarre obsessive thoughts or compulsive acts are experienced as alien to the personality. The problem of differential diagnosis is again one of evaluating total ego function. The greatest difficulties arise with borderline states, in which the problem is largely academic, and severe obsessive-compulsive neurosis.[25, 27, 28]

TREATMENT

As indicated by Hirschberg and Bryant,[48] the various treatment processes and their results have not yet been sufficiently evaluated to secure any general agreement on the most effective methods for helping these children. The treatment plan selected depends on the therapist's ætiological and psycho-dynamic concepts. Thus, depending on how he diagnoses childhood schizophrenia, the therapist will place greater stress on either one or a combination of the following techniques: use of various kinds of somatic therapy; or offering specific relationship gratifications to substitute for the early frustration in the child; or using particular ways of communication in order to strengthen the child's concept of self and non-self; or aiding the child to achieve mastery over his feelings and drives by attempting the further development of preserved ego functioning; or offering a therapeutically designed living experience or group experience to achieve modification of the child's drives and to help him adopt the reality principle; or requiring case-work or psycho-therapy for the parents, concomitant with the child's therapy. Consequently, some way to compare the therapeutic results of the various investigators needs to be developed in order to move forward in this difficult area.

Psycho-therapy with the Child

The methods used vary between the extremes of a supportive relationship and a modified psychoanalysis. Many workers[3, 29, 39, 40, 45, 60, 66, 85, 87] have described in some detail their therapeutic approach to schizophrenic children, and these approaches are in general agreement in several areas. There is the need to accept the child at his own level so as to establish a relationship with him. The child needs help in controlling his overwhelming impulses, and it is necessary to protect him from anxiety.

Psycho-therapy with Parents

As in therapy for the child, the extent and intensity of psychotherapy needed by the parents ranges from a supportive relationship to psychoanalysis.[85, 86, 88, 89] But all parents need some help, since all suffer some confusion, anxiety, guilt, hostility and social isolation.[44, 72]

Some parents receive group therapy, some individual, and others both. Owen[71] treats mother and child as a unit, seeing them together and working directly with the mother-child relationship.

Psycho-therapy Utilizing Special Groups

There has been an increasing tendency in recent years to utilize a special therapeutically oriented day school for the child, which is combined with psycho-therapy for the child and the parents. Rank[78, 79] has described how the nursery school and the teacher act as a continuation of therapy; "as the out-stretched arm of the psychiatrist." More recently other workers have reported on similar programs.[1, 2, 62] Such a program can be effective only when the mother is involved in the total treatment process and is capable of relating with her child and able to assist him in his move towards establishing himself as a separate functioning entity. When practical, fathers should also be offered therapy, and at times this is essential. This type of program may also be combined with some type of group therapy for both parents.

Drug Therapy

Drugs are often useful,[33, 5, 50, 85] particularly some of the anti-histaminics (Benadryl, Phenergan) and phenothiazine derivatives (chlorpromazine, promazine). These drugs have, perhaps, their greatest use in reducing hyperactivity and aggressiveness, disorganized behaviour and unbalanced homeostasis. However, over-activity and aggressiveness may be replaced by more infantile, whining, unhappy behaviour which parents are less able to tolerate, even though the change may enable

therapy to progress faster. Some children who do poorly on one drug may do well on another, even though the drugs are similar in their reported effects. Gravol is of value when body image problems are particularly prominent. Barbiturates are contra-indicated, since they increase perceptual distortion and anxiety. Amphetamines may increase restlessness and are unpredictable, but are useful in aiding control of sexual acting out. The drug which is going to be most effective in any individual case often has to be discovered by trial and error.

Shock Therapy

Electroshock therapy has been used by many workers, but most extensively by Bender and Keeler.[10, 13] They found that the essential schizophrenic process was not modified, but the child benefited in alleviation of secondary symptomatology. There was no interference in development of intelligence, no lasting effects on the electro-encephalogram, and minimal complications. The main indication is paralyzing anxiety of acute onset, and it should be carried out only in an institutional setting where re-patterning of the child's behaviour can be established in a structured milieu.

Lobotomy

In long-standing cases with extreme aggressiveness difficult to control and with a hopeless outlook, lobotomy has been of great help in easing the problems of management.[34, 93]

Institutional and Other Types of Care

Bakwin[5] has recently discussed the home management of these children, utilizing psycho-therapy and drug therapy along the lines already discussed. He recommends institutional care for the child when the parents are too disturbed to become understanding and tolerant, and when school, group and other outlets for the child are unavailable or when the child's behaviour is too excessively disturbed to be tolerated.

Treatment in a residential setting is advocated by many workers, but perhaps most strongly by Bettelheim.[16] In a number of cases, when the possibility of improvement is only slight, the child needs to be cared for in a custodial institution and the family relieved of the burden of his care. In some such cases the parents are unable to give up the child because of their own involvement with him and because of the great anxiety and guilt that separation would involve.

PROGNOSIS

Prognosis is extremely difficult to evaluate, since a number of clinical categories are grouped together as childhood schizophrenia. Further, the condition has been fully recognized for only a comparatively short time which does not permit long-term follow-up studies of a large number of cases.

Kanner and Eisenberg[57] have made follow-up studies on 42 autistic children. In their study the absence of language function by the age of five years was felt to be a reliable criterion of severity of prognosis.

The most extensive follow-up has been done by Bender[11] in which she reports on over 600 schizophrenic children seen between 1935 and 1951. Her findings can be summarized by saying that approximately one-third remained in the community, one-third remained in state institutions, and one-third had had variable periods in the community and in state institutions. Those who remained in the community continuously had mostly made a marginal adjustment both in school and in the family, while only a few could be considered to have made a good adjustment.

Starr[88] has reviewed several factors which might be considered in determining prognosis: the congenital activity type; the nature of the maternal psycho-pathology; the fixation-regression ratio; the psychotic-neurotic ratio; the age treatment began.

As a final word, it is to be hoped that increasingly early recognition of deviations in ego development in young children will go hand in hand with improved treatment facilities. It is only in this way that the ultimate outlook for many of these children can be improved. Early recognition and treatment of ego deviation, even in its milder forms, are essential.

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SPECIFIC READING DISABILITIES

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In a number of children the ability to read is well below their general potential for learning as determined by clinical studies and tests of intelligence. Such children may be regarded as having reading disabilities.

Children may have reading disabilities because of inadequate intelligence, poor physical health or poor teaching. There are some children, however, whose difficulties in reading depend not upon these factors, but upon some factor or factors the exact nature of which is not known at present. These are the children considered to have a specific reading disability, a dyslexia, a developmental alexia or a strephosymbolia (twisted symbols).

SYMPTOMATOLOGY

The histories of children with reading disabilities vary; however, the following may be considered fairly typical histories:

CASE I. John A. was considered a bright and capable child in nursery school and kindergarten. In the kindergarten he had some problems in reading readiness, particularly with those tests which involved recognition of shapes or forms. He showed difficulty in reading from the earliest grades. This was not marked in the first grade, because he was able to memorize the stories and created the illusion that he was reading, but the disability became more evident in later grades.

There was a tendency towards the reversal of letters or words: "b" was mistaken for "d," "p" for "q," "saw" for "was," "dog" for "God," and so on. The reversals were usually horizontal, although on occasion there were associated vertical reversals, "d" being mistaken for "p," and "b" for "q."

He had difficulty with words of all complexities. Compared to children of inadequate intelligence who are able to read the shorter words, he often read the longer words with greater facility because he spent more time in analyzing these words. His errors were frequently found in the simpler words which were read more rapidly, "on" being read for "in," "and" for "the," and the like.

As he grew older, disturbances in spelling and writing complicated his difficulties with reading. In the early grades his difficulty in reading was out of proportion to his difficulties with other subjects, particularly arithmetic. In later grades, however, he

began to have difficulty with arithmetic because he could not read the problems and became confused about the questions. English, Social Studies and History, subjects which required a great deal of reading and memorization from the texts, were particularly difficult. In the higher grades he found it increasingly difficult to complete the longer assignments and essays.

The difficulties in reading were unexpected, and he was placed under considerable pressure by teachers and parents because they considered him lazy and disinterested. Unfortunately for this boy, 6 years elapsed before the condition was recognized and attempts made to correct it.

Many children with specific reading disabilities show associated disturbances in allied subjects such as spelling and writing. In addition, some children show disturbances in the area of speech and general motor skills. Some authors believe the term "specific language disabilities" should be used rather than "specific reading disabilities" because of the frequent involvement of various aspects of communication in either the child or his family.

CASE II. Peter B. had great difficulty with spelling, frequently misspelling the simplest words. His mistakes were not only numerous, but frequently bizarre with reversals, omissions and confusions of letters and, on occasion, mirror writing with the reversal of letters and words. He frequently substituted letters, writing "n" for "m," "v" for "w," and so on. The basic disturbance appeared to be a poor visual memory with an inability to recall the individual letters in the correct order of their presentation. He not only spelled incorrectly, but also failed to recognize his mistakes.

CASE III. Arthur C. was an extremely slow writer, spending a great deal of time writing in order to avoid mistakes. His writing was poor, almost illegible, and he was frequently unable to complete his assignments. In the classroom his oral responses to questions were at a much better level than his written responses to the same questions.

CASE IV. Nancy D., though physically and intellectually normal, did not develop speech at the usual time. She showed no disturbance in the comprehension of language and developed remarkable skills in communicating with her family through gestures and mimicry. When language did develop, it was indistinct with frequent substitutions of consonants. Even after the development of adequate articulation there seemed to be a slight limitation in verbal communication, and at times she seemed to grope for words, giving the impression of a mild aphasia. In general, the speech disturbance found in the families of children with specific reading disabilities is more frequently a disturbance in the development of language or in the clarity of articulation rather than stuttering or stammering.

CASE V. William E. showed clumsiness and general awkwardness in his physical activities. Clinically, the picture suggested a mild degree of cerebellar inco-ordination, but his physicians hesitated to diagnose a specific disease of the central nervous system. They felt that he represented the reverse of the constitutionally well co-ordinated athletic person. As one would expect, he had difficulty in games, particularly those which involved the co-ordination of hand and eye.

FREQUENCY

It is difficult to obtain accurate figures, but it has been estimated that from 10 to 15 per cent of children in American schools have difficulty reading at the proper grade level and that 1 to 2 per cent have

a serious reading disability.[7] It occurs three to four times as frequently in boys as in girls.

ÆTIOLOGY

At first specific reading disabilities were thought due to physical lesions, but now are thought due to either disturbances of lateral dominance or to emotional factors. In the literature there are numerous reports of physicians associating specific language and reading disabilities with dominance, and psychologists and educators rejecting the concept of dominance in favour of an emotional origin.

Among the various reasons considered at the present time responsible for specific reading disabilities are the following:

Maturation

In some children the disturbance in reading appears to be a maturational or developmental lag. These children are not ready to read at six years of age, and may not reach this stage of development until they are seven or eight. With the ordinary methods of instruction they gradually develop the ability to read, and to make adequate progress in reading.

Organic Cerebral Disease

It has been postulated that this condition may be associated with a lesion of the angular gyrus of the dominant temporal lobe, since in adults such a lesion produces a disturbance in reading.* There is little proof, however, of such organic disease in children with reading disabilities, and complete neurological and electro-encephalographic examinations of these children are usually negative. It has been suggested,[8] however, that an injury in the pre-natal or perinatal stages of life may produce damage that cannot be detected clinically, yet may interfere with the acquisition of reading.

Disturbances of Vision

In children with reading disabilities refraction usually reveals normal visual acuity. It has been suggested, however, that the reading

* Recent studies[10] would indicate that the cerebral hemisphere, which contains the dominant centre for handedness, may not be the dominant centre for speech or reading. In the past it had been assumed that the dominant hemisphere for hand skills was the dominant hemisphere for speech and reading. This may not be true, and these centres may be in opposite hemispheres. In general, however, it appears that the dominant centre for speech is usually in the left cerebral hemisphere no matter whether the patient is right-handed, left-handed or ambidextrous.

disability may be due to an inadequate fusion in the fields of vision, or a disturbance of motor function which prevents the eyes from sweeping smoothly across the page. Children with reading disabilities usually read with jerky movements, pauses and, on occasion, backward movements. This, however, is felt by most to be due not to a specific motor disability, but to a disturbance in perception, and the abnormal movements are thought to be due to the inability to comprehend the written material. The letters are clearly seen, the eye muscles are capable of normal movements, but the difficulty lies in the ability to recognize and interpret the letters and words.

Teaching

There seems to be no doubt that specific reading disabilities occur more commonly with the present methods of teaching. The method most frequently used to teach reading, the sight or flash-card, produces more reading disabilities than the older phonetic method. In the sight method the child is taught to recognize the word on the card as a whole word, a pattern or *gestalt*. He is not taught to analyse the word by syllables and to sound out each syllable. The advantages of this method are that it arouses earlier interest in reading and teaches reading with greater rapidity. On the other hand, it produces greater disturbances of reading in certain children and a higher percentage of children with obvious reading disabilities. Reports from countries which use a predominantly phonetic system, such as Germany, indicate fewer reading disabilities. The present feeling is that the sight method brings out those children who have potential disturbances in reading which might not be revealed by the phonetic system.

Disturbances of Dominance

This concept is based upon the theory that the development of reading requires that one cerebral hemisphere be dominant and that the child must suppress the mirror image in the non-dominant hemisphere before he can read satisfactorily. The disability is believed to be due to a struggle between the two cerebral hemispheres for such dominance. Children with reading disabilities have a high incidence of such disturbances as right-handedness and left-eyedness, left-handedness and right-eyedness, or ambidexterity. One may also find parents and siblings with a similar history.

Eustis[5] found that only four of 22 children with reading disabilities were entirely right-handed, 18 being ambidextrous. Twelve children were right-eyed, five were left-eyed, five ambi-eyed, and seven showed crossed laterality with the preferred eye on the opposite side to the

preferred hand. In 18 of the 21 families there was a history of left-handedness, ambidexterity or language difficulties in other members of the family.

Creak[4] found that 24 per cent of a group of 50 children with reading disabilities were right-handed and right-eyed. Twelve per cent were left-handed and left-eyed, and the remainder either ambidextrous or with crossed handedness and eyedness. Eight of these showed a delay in the onset of speech, and two had problems in auditory discrimination, with confusion of spoken words. There was a family history of left-handedness or reading disabilities in 34 per cent of the group.*

Emotional Disturbances

Considerable controversy has developed over the relation of emotional disturbances to specific reading disabilities. Some consider these emotional disturbances to be the primary cause for the reading disability, and others consider that the emotional disturbances are secondary to the reading disability itself.

Blanchard[2] believes that about 20 per cent of these disabilities are due to emotional disturbances. Since a fairly high level of emotional adjustment is a prerequisite for reading readiness, emotional maladjustment will prevent the child from reading. Fabian[9] found that 10 per cent of the children in the third grade classes of a New York school had reading difficulties. Of these children, 11 had reversals, and the general clinical pictures suggested specific reading disabilities. Most of the children had severe behaviour problems which arose from disturbed home situations.

Creak[4] reported distractability, restlessness, a lack of interest in reading with a general aversion to school. Gallagher[7] noted that children with these disturbances were often anxious and unhappy because they were unable to do their work at school as well as their peers did, and were considered failures by teachers and parents. Conscious of their difficulties, they approached reading with an expectation of failure. In some families the emotional problems were aggravated by other siblings who were free from such disabilities and were able to work at a much higher level of efficiency. This was particularly true when a younger sibling entered the same grade as the child with the reading disability.

In a number of children the primary difficulty in reading arises from emotional disturbances. Some are children who have been over-protected and who, because of their immaturity, are unable to meet the

* General figures of dominance suggest that left-handedness occurs in 5 to 10 per cent of the general population, with an average around 7 per cent. There has been no attempt, however, to study the incidence of ambidexterity in the general population, and no definite figures are available for this condition.

normal problems of the classroom, tending to withdraw and failing to work through their difficulties. Some are children with conflicts and hostilities at home who transfer those conflicts to the program of the school. Many of these children, however, do not show the typical patterns of the specific reading disabilities, and most of them will eventually develop adequate reading skills.

In some cases the emotional disturbance is secondary to the specific reading disability. The reaction of the child will depend upon the degree of pressure placed upon him, and also upon his basic temperament. Some will react aggressively, refuse to work, and are disobedient and difficult to control in the classroom. Others will respond passively, give up and fail to work up to the level of their actual ability.

It is unusual to find older children with specific reading disabilities who have not an associated emotional disturbance. It is important that this be recognized, because the therapeutic program must be directed not only towards the specific disability, but also towards the emotional disturbance produced by that disability. In some older children the emotional disturbance requires the more intensive programme of therapy.

DIAGNOSIS

A specific reading disability should be suspected in a child who has difficulties in reading that are out of proportion to his difficulties with other subjects. The investigation of these children usually involves the following programme:

A *complete history*, with an attempt to determine the quality of the teaching and the relationship between the child and the teacher.

A *complete physical and neurological examination* to determine any organic disease which might be responsible for the disability, with an electro-encephalogram or a pneumo-encephalogram if indicated.*

An *assessment of intelligence*, usually through the Stanford revision of the Binet-Simon or the Wechsler Intelligence Scale for Children.

A *complete appraisal of reading ability* through such tests as the Gates Primary Reading Test, the Gates Sound Reading Test, the Gray's Oral Reading Test, the Nelson-Denny Reading Test for Senior High Schools and Colleges, and the Minnesota Speed of Reading Test for College Students.

An *analysis of handedness and dominance* by such tests as Durof's Handedness Test or the Tests of Abram Blau.[3]

An *assessment of the emotional reaction* of the child to his reading difficulties and the relative importance of these emotional disturbances

* In some clinics the ophthalmograph is used to check vision, stereognosis and ocular imbalance.

to the reading disability. This is best done through a detailed history, although additional information may be obtained by such psychological tests as the Rorschach or the Children's Thematic Apperception Test.

As a result of such investigation one can usually decide whether the child has a reading disability and, if so, whether that disability is a specific reading disability.

PROGNOSIS

It is impossible to give an accurate answer to this question, since few adequate studies have been carried out in these children. From general clinical experience, however, the children seem to fall into the following groups:

GROUP I: CHILDREN WITH A MINOR DISTURBANCE. These usually work through the disturbance, gradually developing normal reading maturity in later years.

GROUP II: CHILDREN WITH A MODERATE DISTURBANCE. Most children lie in this group, and the limitation, though not sufficient to alter their education, makes their studies more difficult. They usually require a special programme of remedial reading and may lose a year in the early grades.*

GROUP III: CHILDREN WITH A SEVERE DISTURBANCE. These often continue to have difficulties in spite of remedial reading. In some children the disability remains as a permanent and limiting factor in their education, forcing them to take a technical course rather than an academic course.

It may be necessary for the parents of some of these children to accept the fact that their children, even though of normal or superior intelligence, will be limited in their ultimate education by the reading disability. This is often hard for parents with a college education, who find it particularly difficult to accept such limitations upon the education of their children.

PREVENTION

Most teachers use only a single method of teaching reading: the sight method, which calls for perfect reasoning, accurate and instantaneous focusing, and a good visual memory. Many specific reading disabilities could be prevented if teachers had at least two different methods for teaching reading, one for the visually minded child and one for the auditory-minded child.

* Lectures this year to the second and third year medical students brought forward 12 students with a history of specific reading or spelling disabilities in earlier life. In several students there was still some evidence of these disabilities, particularly slowness of reading and difficulty with spelling.

Though ambidexterity seems to play a definite part in the development of reading disabilities, there is little proof that the facilitation of unilateral dominance in such children definitely improves the development of reading. There is general agreement, however, that once dominance is definitely established, it should not be altered.

TREATMENT

The most important aspect of treatment is early recognition by the teachers in the primary grades at school. Since, however, many teachers and even principals are unfortunately unaware of this condition, it may be the physician who first suspects a reading disability. It is then his responsibility to see that these children have further investigation and that the results of that investigation are made available to the school.

In mild cases, particularly those in which the problem appears to be one of delayed maturation, little need be done except to recognize the condition and to reduce the pressures upon the child. One must await maturation, and specific remedial techniques are often of little value. These children gradually develop adequate reading facilities in later grades.

In moderate cases the problem is frequently solved by an approach to phonetic reading. The children must begin by the recognition of individual letters followed by individual syllables and words. It is often necessary to go back to the primary grades and to carry the child through those grades up to his present grade.

In severe cases special methods are necessary. One of the most effective is the kinesthetic method of Grace Fernald,[6] using a threefold sensory approach to reading. In this method the child sees a word, hears the sound of it, and traces out its shape with his finger. This method is often successful with children who have been unable to learn with the phonetic system.

The atmosphere in which remedial reading is taught is most important. Teachers who deal with specific reading disabilities must be tolerant, patient and able to develop an interest in reading and a sense of achievement in their students. Attempts by parents to teach their children usually meet with failure, either because the parents are unskilled in teaching or because they become emotionally involved in the child's difficulties.

In some children orthoptic equipment may be used to develop increased speed in reading. Though such equipment appears of proved value in adults, it is of doubtful value in children.

Many children require help for their emotional difficulties. If the problems are not too complex, the family physician or the pædiatrician

may be of help. When the emotional disturbance is marked, it may be necessary to involve the child and his family in a more intensive therapeutic programme through a child psychiatrist or a child guidance clinic.

In many areas the problem of specific reading disabilities has not been adequately met by the local boards of education. In some communities, however, special classes are available, and children with reading disabilities are enrolled in these classes until their reading improves. In other communities special reading consultants work with teachers on individual cases. In this way help can be given to a larger number of children, although the quality and degree of help available to those children are less than can be obtained from a single class. In other areas special schools for remedial reading have been developed. In some the child receives all his education in these schools; in others he attends the school for a few hours each day, taking the rest of his education in his regular school.

CONCLUSION

Approximately 10 to 15 per cent of children in North American schools have difficulty in reading up to the proper grade level. Some of these children, perhaps 2 to 5 per cent, represent specific reading disabilities due to disturbances in dominance and/or emotional disturbances. It is important to recognize these children in the early grades, to reduce the pressure upon them, and to provide them with a suitable programme of remedial reading. Unfortunately, many of these children are not recognized and treated because many teachers and schools are unaware of the condition.

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THE DOCTOR AND ADOPTION

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No individual or agency has, as yet, evolved an ideal framework for adoption practice. Vast cultural, racial and religious differences, which continue to separate men, make it unlikely that such a universal ideal will be achieved in our lifetime. One recent study[21] made apparent the extreme variability in this regard from agency to agency in the same state as well as in widely separated states in the United States of America. There is ample evidence of concern about the problem, and a widespread desire to improve adoption practices, especially for the benefit of the child. This is shown by the fact that within the last four or five years conferences and official publications on the subject have been arranged by agencies of the Government of the United States[17] and the Government of the United Kingdom,[20] an independent national welfare organization[21, 22] and by a national organization of the medical specialty most concerned.[13] An excellent bibliography appears in one of these publications,[21] and should be consulted by anyone wishing to pursue the whole subject, or especial aspects of it, in more detail.

A study of these publications reveals that the doctor's rôle in adoptions can be much more complex than most of us would have suspected. It also becomes obvious that there are certain major functions which are most decidedly not performed by the doctor. Since there may be some medical men who are still unwilling to accept this latter premise, we will begin by emphasizing two aspects of it.

WHAT THE DOCTOR'S ROLE IN ADOPTIONS DOES NOT INVOLVE

1. *No doctor can decide, by himself, that any child is not adoptable.* Many agencies still refer children for examination with the request that the examining physician give an opinion regarding "adoptability." If he believes that this is not his function, the physician will not

attempt to answer this question. He will give rather a report on the child's current physical and developmental status in the light of what he knows about its inheritance, the pregnancy, birth and newborn course and the way it appears to have been handled by those caring for it up until the time of his examination. Whether or not the child is adoptable should be decided by appropriate adopting parents with the help of an officially recognized, well-administered adoption agency.

A simple definition of an adoptable child is "one who is legally free and who can benefit from family life."[21] This concept has been elaborated more recently as follows: "Any child can be considered adoptable who can gain from family life and who has the capacity to develop in a normal environment, and for whom a family can be found who will accept him with his history and capacities. His history and examination should be such that there is reasonable assurance that the child has ability and potentialities for adjustment, that his handicaps are not such as will interfere with development of a sound child-parent relation. He should have the capacity to find and give satisfaction in family living and not require a kind of care which no parent is expected to be able to give."[13]

This is a difficult concept for many doctors to accept. Some reject it, although they are quite prepared to accept and make the most of the potentialities of their own natural children, and do not call on God or their obstetrician to guarantee a specific sex, complexion and physique, superior intelligence and curly hair. Since there may be as many as 10 applications for an adoptive child for each placement made,[17] many who would have made superior parents are denied the opportunity. They may remain unwillingly childless in spite of the presence in their community of many children with physical or other handicaps who are denied the opportunity to grow in a family. Recent experiences with placement of such children (often still called unadoptable)[2] have demonstrated that they can gain from family life. Adopting parents who take such a child, knowing his limitations, experience a much fuller life than would otherwise be theirs. Their recognition of this is shown by the fact that they go ahead with adoption after the agency's supervisory period. Often their attachment to the child is strengthened by the experience of sharing his care during surgical correction of a disability (such as a heart anomaly).

2. *The doctor's function does not include the selection of the adopting home and the placement of a child in it.* Successful placement is beyond the capacity of any one practitioner of any one profession. It involves close liaison and understanding among doctors, lawyers and social workers. This cooperative effort can be best arranged by officially recognized adoption agencies. As Reid[19] states: "The fact that thousands of adoptions arranged by well meaning individuals have turned

out successfully is no more argument against the necessity for social agencies than is the fact that thousands of deliveries made in homes without accident is an argument against hospital confinements." He further points out how only such an agency can handle all the complexities involved, through its use of individuals from several disciplines—"social workers, trained and experienced in such matters as understanding the motivations and conflicts of the unmarried mother, interviewing and obtaining comprehensive and accurate social histories of adoptive applicants, a thorough knowledge of the laws pertaining to adoption, and knowledge of the utilization of other disciplines; psychiatrists, who can help with such problems as are involved in difficult questions of the motivation of some adoptive parents, questions concerning the probable adjustment of older children who have suffered emotional damage and who may or may not be able to accept or be acceptable to the average family; geneticists, to advise on questions of heredity; lawyers, thoroughly acquainted with the myriad legal questions surrounding adoption; psychologists, who in spite of the overwhelming evidence of the inadequacy of infant testing for predictive purposes, still have an important place in the clinical examination of children prior to adoption; and the several other disciplines such as anthropology, sociology and religion." The study of Amatruda and Baldwin[1] tended to demonstrate the much higher incidence of satisfactory placement by such an agency as against those arranged "independently." Not the least of the disadvantages of the independent placement is the fact that the natural mother often knows the whereabouts of her child, and even though she may not plague the adopting parents, they may constantly fear that she will.

WHAT THE DOCTOR'S FUNCTION IN ADOPTIONS MAY INCLUDE

A pædiatrician's most important function in adoptions is the preadoptive appraisal of the child (for the agency or for the adopting parents), and frequently thereafter the medical supervision of its care in its new home. The doctor plays many other important rôles and, whether pædiatrician, general practitioner, obstetrician or psychiatrist, has concern not only with the child, but also with its natural parents, its adoptive parents, the placement agency and, as a citizen, with society.

The Natural Parents

The unmarried mother, or married parents who wish to give up a child, may approach first their family physician or some other member of the medical profession for help and advice. He is naturally interested

in the health of both parents and their inheritance and the state of the mother throughout the pregnancy. Whether he be psychiatrist or not, for the sake of their future happiness he is concerned with their reasons for becoming unmarried mothers and unmarried fathers, or married parents who wish to give up a child.[12, 14] He may recognize in one or the other of them signs of psychiatric illness for which early referral for further study and treatment is urgent. In any event, if he accepts the fact that he is not the one to do the placement, he refers such prospects to the appropriate agency in his community as early as possible. It is important that he should recognize the difficulties for mother and child that are inevitable if she plans to keep the child, but he ordinarily leaves to the agency the complicated task of explaining these problems to the mother and helping her make the decision (which is hers) whether or not to give up the child for adoption. There is no need to emphasize that it is the responsibility of doctors in every community to see that adequate facilities are available to give as complete pre-natal and natal care to such mothers and their babies as is provided for any other pregnant woman and her child.

The Adopting Parents

Too often doctors have become involved in adoption because of some presumed benefit that may accrue to the adopting parent. Most now realize that if a child is placed primarily to hold a marriage together, or with the hope of preventing psychiatric breakdown in the mother, not only are these hopes frequently dashed, but also a great disservice may be rendered to the helpless child so placed. Increasingly there is a recognition of the fact that adoption is "not finding children for parents—but finding parents for children."[19] Because of his concern about the future welfare of the child, especially if he is going to provide health supervision for it, it is helpful for him to discover, if he can, how capably these parents may cope with various problems which will arise. It is, of course, extremely difficult even for those with especial training and long experience to predict how parents will manage when they have never had the opportunity to care for a child. Most parents show considerable capacity to develop with the child, whether they be natural parents or adopting parents. No adopting parent is a perfect parent, and no adoptive placement is a perfect placement.

The frequency of severe personality disorder in so-called unadoptable children who have suffered frequent change of foster home or institution, or prolonged institutional care,[3, 10] points up another rôle of the physician. This is the recognition of the presence in certain potential adopting parents of an ability and a desire to care for such a handicapped child, bearing in mind the possibility that "any child is adopt-

able when a couple can be found that is willing and capable of meeting his needs."[13]

Besides routine pædiatric care, he may offer help to them as to how best to make the child aware of the fact that it is adopted. The British Report urges that it be required of adoptive parents "that they bring up the child in the knowledge that it is adopted."[20] This is now a commonly accepted tenet, but it may actually be overdone. It has been suggested that adoptive parents are being somewhat less than truthful if they tell the child he was "chosen" when actually they may have had only one chance to accept only one child. If they admit this to the child, he is less likely to suggest they should have "chosen" someone else, when later on they may find fault with his behaviour. They may also need help in accepting the fact that their attitude towards an adopted child may differ from feelings they would have had, or may have, toward a natural child. They should be advised against blaming on the child's unknown ancestry, behaviour which may well have been produced by the way they have handled him. This is a tendency perhaps more common among neighbours and relatives than among adoptive parents themselves. They may also desire advice as to the possibility that their previously infertile union may become fertile as a result of the adoption.[7] Perhaps the safest answer (after adequate investigation as to the cause of the sterility) is that the "literature affirming the therapeutic effect of adoption on infertility is speculative and without proof."[11]

The Adoption Agency

One would hope that enough has been said already to produce at least favourable consideration of the idea that placements should be made through an adoption agency. Physicians who are in any way concerned with adoption owe it to themselves and their patients to become aware of the agencies in their communities and to see that they are effectively staffed and adequately financed. When called upon to give help in their professional capacity, they will ensure more effective functioning of the agency by doing so to the full measure of their ability. If they are dissatisfied with the way agency placements are being arranged, they should outline their objections to the administrative officers concerned.

Society

If it is true that every child has a right to grow in a family, and if it is true that "any child is adoptable when a couple can be found that is willing and capable of meeting his needs," and if it is true

that children who do not have this opportunity are more prone to serious psychiatric illness and personality disorder and hence fail to contribute adequately to the community, then the doctor, through his activity in his profession, and as a citizen, should make every effort to see that adoptions are facilitated through the appropriate channels. The most successful placement for child and parents is probably made before the child is six months old. However, more and more emphasis is being placed on the worth of adoptive placement of older children, of handicapped children and of children of mixed background or with parents of minority races or nationalities. It is generally recognized that natural parents have the right to state the religion they prefer for their child. When placement with adoptive parents of this religion is not possible, one would agree with Polier[16] that "no person or religious institution, no public department and no state, has the right to say to a defenceless child, 'You have no home, but because of your race or religion you shall stay in an institution until you are 16 or 17 years, and then be turned out into a world in which you have no one to whom you belong.'"

The Child

Every physician should recognize that the child who is available for adoption has the right to be placed in the "best" of as many as 10 homes which want him, and that this best home is not necessarily that of a "friend of a friend" of the physician. The child should also have the right to be placed early (if possible in the newborn period).[6] However, the development of an awareness of the change in environment involved in adoptive placement (in the second half of the first year) does not necessarily of itself lead to serious disturbance in a child who is placed after six months, especially if he has been in an understanding foster-home before this.

The physician examining a child pre-adoptively owes it as complete an examination as he will give to any other child he sees in his practice. This includes not only a complete physical assessment with especial emphasis on the adequacy of special sense organs (eyes and ears), but also an appraisal of the child's developmental status.[4, 5, 9, 18] The adoptive parents may thus be adequately informed, and any correctable abnormality that is discovered can be treated. He should avoid making positive predictions as to future physical and mental capacity,[23] which cannot really be made until the child reaches adulthood, but is justified in giving a qualified impression as to what the future holds in the light of current findings and a knowledge of the child's background. To quote Penrose:[15] "A knowledge of medical

genetics will merely aid the physician in his search for obscure diseases and he will make a particularly careful examination of the child's urine, blood, eyes, skin, etc. Many behaviour disorders and physical illnesses which are influenced by heredity to a noticeable degree do not have their onsets until later on in life, and it is usually concerning these that the Geneticist is asked to give an opinion." The child as well as the adoptive parents has the right to know, so far as one can inform him, the possibility that recessive disease may develop later in life. "Diseases falling into this class include certain types of epilepsy, nervous degenerations and myopathies but not, as sometimes stated, schizophrenia."[15] He should be aware of the existence of a rare dominant abnormality in a close relative, especially if it is his own parent, and if, for instance, this is Huntington's chorea, there is about a 50 per cent chance that the child will have the disease after the age of 35 years. This is one of the few socially significant diseases inherited in this manner. The suggestion that manic depressive psychosis is due to a single dominant gene is "very far from being established." Penrose concludes: "If accurate records of adoption cases are made available for scientific study more frequently in the future than has been done in the past, in succeeding years the effects of environment upon physical and particularly upon mental traits may be better understood than they are today."

Fraser's[8] article on Parent Counselling in Some Common Pædiatric Diseases (p. 475) should be consulted for more detailed information on this subject.

SUMMARY

This outline has reviewed some aspects of current practice and writing on the subject of adoptions, with emphasis on the functions that may be performed by the physician. His services may include not only pre-adoptive and follow-up examination of the adopted child, but also medical assistance and advice to the natural parents and to the adopting parents. He recognizes that he cannot work alone in the field, and cooperates with officially recognized adoption agencies, their workers, and other professionals in the field. His opinion about the child to be placed is best confined to a statement as to its status on the basis of his examination and his knowledge of its background, taking care to avoid making unwarranted positive predictions about its future. The question of the "adoptability" of any child should probably be decided by appropriate adopting parents on the advice of, and with understanding supervision by, the adoption agency.

Current trends in the field emphasize the rights of the child to grow

in a family. Future research should concentrate on the degree to which these recommended practices have led to successful placement from the point of view of the child, the adopting parents and society.

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THE USE OF DERMAL CONFIGURATIONS IN THE DIAGNOSIS OF MONGOLISM

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A preliminary discussion of the use of dermal configurations in the diagnosis of mongolism was published about a year ago.[5, 6] When offprints of the article were used as the basis for laboratory exercises with pre-medical students in a course in Human Genetics, it was soon evident that the outline could be considerably clarified. Each student was asked to submit suggestions, and a number of these have been incorporated in the present paper.

As previously pointed out, it is frequently difficult on the basis of clinical evidence to reach a decision as to whether or not a child is a mongoloid imbecile, particularly in the case of a newborn infant. Any additional evidence that can be used is therefore most desirable, especially if this evidence is purely objective. Exactly this sort of objective evidence is to be found in an analysis of the finger, palm and sole patterns, which vary significantly in their frequencies for mongoloid imbeciles as compared with a control series. This paper develops a method by which one can arrive objectively at a calculated index or score. The method is illustrated by calculations based on studies of 200 certified mongols (the majority of whom are living in institutions) and 500 members of a control series. It will be shown that more than 70 per cent of the mongoloid imbeciles possess combinations of patterns not repeated in the non-mongol, while more than 68 per cent of the non-mongols have combinations not found among the imbeciles.

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EMBRYOLOGICAL DEVELOPMENT OF DERMAL CONFIGURATIONS

The dermal configurations are formed at the sites of mounds present during the early months of fœtal development. These mounds are situated on the tips of the digits, in the four interdigital areas of the palm and sole, as well as in the thenar and hypothenar areas. In addition, there is on the sole the calcar mound. During the third and fourth fœtal months the mounds are receding at the same time as the dermal ridges are being formed. The interplay of the two processes gives rise to the distinctive patterns found in these areas.[3] Disturbances of fœtal growth during the third and fourth months are recorded in the configurations. The configurations, once established, never change (except in size) during fœtal life to birth, nor from birth to death.

METHODS OF PRINTING AND FORMULATION

Inkless methods of printing infants were outlined by Walker.[6] More recently an excellent new method has been devised by the Hollister Co.,* which for young and newborn infants is superior to any other.

A basic discussion of the formulation of dermal configurations is to be found in the text by Cummins and Midlo.[3]

DIGITAL PATTERNS

For convenience the digital patterns are here classified into four types: arch, loop ulnar, loop radial, and whorl. The whorls include

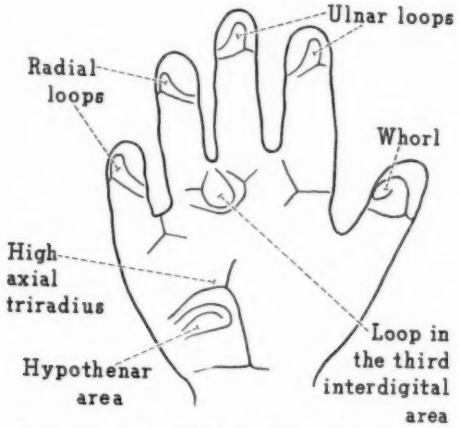

Fig. 52. Outline of palm of a mongoloid imbecile, showing certain digital and palmar patterns. (*J. Pediat.*, Vol. 50.)

* Materials can be purchased from Franklin C. Hollister Co., 833 North Orleans Street, Chicago 10, Ill., U. S. A.

double loops and all patterns with two triradii (see Fig. 52). A triradius is the meeting point of three dermal ridges or radii, forming three angles of approximately 120 degrees each.

In a random series of normal persons it can be clearly demonstrated that each digit of each hand has a different distribution of patterns (Table 22). The second digit (or forefinger) is the most variable,

TABLE 22. *Comparison of Percentage Frequencies of Digital Patterns of Mongoloid Imbeciles and Controls*

PATTERN	V		IV		III		II		I	
	Mon.	Con.	Mon.	Con.	Mon.	Con.	Mon.	Con.	Mon.	Con.
Left Digits										
W	18.3	12.0	32.8	36.9	13.6	17.4	11.9	33.4	22.4	30.8
U	77.1	85.4	58.7	60.2	83.5	71.4	82.4	36.3	73.0	62.7
R	2.9	0.1*	5.1	0.9	1.7	2.6	2.3	19.4	0.6	0.8
A	1.7	2.6	3.4	3.0	1.1	8.6	3.4	10.9	4.0	5.8
Right Digits										
	I		II		III		IV		V	
W	25.9	38.6	14.9	35.7	11.3	18.4	31.8	46.6	18.9	14.6
U	70.6	57.3	82.3	31.1	86.4	70.9	60.2	52.0	75.4	84.0
R	0.1*	0.8	1.7	20.3	1.1	3.4	5.7	0.3	4.6	0.3
A	3.5	3.3	1.1	12.9	1.1	6.3	2.3	1.1	1.1	1.1

Percentages for mongoloids based on the finger patterns of 177 imbeciles, 54 of whom were reported by Cummins;[2] percentages for controls based on a random group of 328 subjects. Sexes approximately equal in both groups.

Symbols: *W*, whorl; *U*, loop ulnar; *R*, loop radial; *A*, arch.

* Value assigned for purpose of calculating the index, since the observed frequency was 0.

showing in this particular series the following percentage frequencies of patterns on the left hand: whorl, 33.4; loop ulnar, 36.3; loop radial, 19.4; arch, 10.9. The fifth digit is the least variable: whorl, 12.0; loop ulnar, 85.4; loop radial, 0.0; arch, 2.6.

The distribution of the digital patterns on each of the 10 fingers of mongols compared with normals shows marked differences, with an over-all increase in ulnar loops, as well as an increase in radial loops on the fourth and fifth digits (Table 22).

Differences in the frequencies of patterns can be demonstrated on the left forefinger as follows:

PATTERN	MONGOLS	CONTROL
Whorl	11.0	33.4
Ulnar loop	82.4	36.3
Radial loop	2.3	19.4
Arch	3.4	10.9

The argument and method used throughout the paper can now be illustrated. The argument is this: The probability that a child is a mongoloid imbecile is dependent upon the ratio of the frequency of the patterns in mongols and in controls. The greater the ratio, the more likely is it that the subject who exhibits the characteristic is a mongoloid imbecile. This ratio may then be taken as an index of the "probability." For example, take one finger of a person (such as the

TABLE 23. *Ratios Based on the Frequencies of Mongoloid/Control Digital Patterns*

PATTERN	LEFT DIGITS					RIGHT DIGITS				
	V	IV	III	II	I	1	II	III	IV	V
W	1.53	0.89	0.78	0.36	0.73	0.67	0.43	0.58	0.68	1.29
U	0.90	0.97	1.17	2.27	1.16	1.23	2.65	1.22	1.16	0.90
R	29.00*	5.67	0.65	0.12	0.75	0.13*	0.08	0.32	19.00	15.33
A	0.65	1.70	0.13	0.31	0.69	1.06	0.09	0.17	2.09	1.10

Symbols: *W*, whorl; *U*, loop ulnar; *R*, loop radial; *A*, arch.
* Based on an assigned value, as in Table 22.

TABLE 24. *Ratios Based on the Frequencies of Mongoloid/Control Digital Patterns, Expressed as Logarithms*

PATTERN	V	IV	III	II	I
			Left Digits		
W	+0.18	−0.05	−0.11	−0.44	−0.14
U	−0.05	−0.01	+0.07	+0.36	+0.06
R	+1.46*	+0.75	−0.19	−0.92	−0.12
A	−0.19	+0.23	−0.81	−0.51	−0.16
			Right Digits		
	I	II	III	IV	V
W	−0.17	−0.38	−0.24	−0.17	+0.11
U	+0.09	+0.42	+0.09	+0.06	−0.05
R	−0.89*	−1.10	−0.49	+1.28	+1.19
A	+0.03	−1.05	+1.23	+0.32	+0.04

Symbols: *W*, whorl; *U*, ulnar loop; *R*, loop radial; *A*, arch.
* Based on an assigned value, as in Table 22.

left forefinger), and if the pattern on this finger is an ulnar loop, then the ratio is 82.4:36.3, or 2.27. Should the pattern be a loop radial, the ratio is 2.3:19.4, or 0.12. Similarly, the argument follows for the other patterns of this digit and for the remaining digits (see Table 23). It is assumed that the occurrence of each pattern on the 10 digits is an independent event. For ease in calculations of the product of the 10 indices and for recording in histograms, the ratios given in Table 2 are expressed as logarithms in Table 24. The latter are cited as either posi-

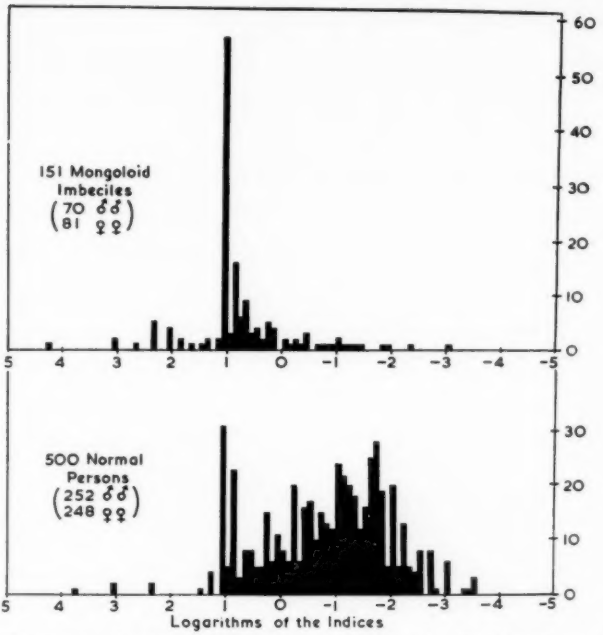

Fig. 53. Histograms showing distributions of indices for the digital patterns alone of 151 mongoloid imbeciles and 500 controls.

tive or negative logarithms. A histogram based on the digital patterns alone is shown in Figure 53.

PALMAR CONFIGURATIONS

Of the palmar patterns, those of two areas are particularly useful. The first concerns the size of the hypothenar patterns as measured by the height of the distal axial triradius. In general, one may say that 85 per cent of the palms of mongoloid imbeciles have a large hypothenar pattern terminated distally by a high axial triradius (t″) (Fig. 52). A pattern of this size is found in about 12 per cent of the palms of non-mongols.

To determine the position of the distal axial triradius, measurements are made (1) of the distance between the triradius and the distal wrist crease, (2) of the length of the palm from the distal wrist crease to the proximal crease of the middle finger. The height of the triradius is then calculated as a percentage of the palm length. Triradii in low positions, from 0 to 14.9 per cent, are symbolized by *t*; those in

intermediate positions, from 15 to 39.9 per cent, as *t'*; those in high positions, from 40.0 per cent and up, as *t''*.

Unilateral distributions of the axial triradii are summarized in Table 25, which gives also the calculated ratios. The logarithms are in Table 26.

The second palmar configuration is that present in the third interdigital area (Fig. 52). Conventionally, six patterns are recognized in this area, but since the formulations of vestigial patterns compared with "open fields" tend to be subjective rather than objective, we

TABLE 25. *Comparison of Percentage Frequencies of Heights of Palmar Axial Triradii in Mongoloid Imbeciles and Controls*

HEIGHTS OF AXIAL TRIRADII	PERCENTAGE FREQUENCIES				RATIOS OF MONGOL/CONTROL	
	Left Palm		Right Palm		Left	Right
	Mongols (161)	Controls (255)	Mongols (161)	Controls (255)		
Low (0–14.9%) (t) and intermediate (15.0–39.9%) (t')	14.2	89.8	15.6	86.7	0.2	0.2
High (40.0% and over (t'')	85.8	10.2	84.4	13.3	8.4	6.3

TABLE 26. *Ratios of the Frequencies of Mongoloid/Control Palmar Axial Triradii, Expressed as Logarithms*

HEIGHTS OF AXIAL TRIRADII	LEFT	RIGHT
Low (0–14.9%) (t) and intermediate (15–39.9%) (t')	−0.70	−0.70
High (40.0% and over) (t'')	+0.92	+0.89

TABLE 27. *Comparison of Percentage Frequencies of Third Interdigital Configurations in Mongoloid Imbeciles and Controls*

CONFIGURATIONS	PERCENTAGE FREQUENCIES				RATIOS OF MONGOL/CONTROL	
	Left Palm		Right Palm		Left	Right
	Mongols (150)	Controls (1000)	Mongols (150)	Controls (1000)		
True patterns:						
Loop (L)	54.0	31.3	85.4	55.5	1.7	1.5
Loop with accessory triradius (D)						
Whorl (W)						
Not true patterns:						
Loop vestigial (L^v)	46.0	68.7	14.6	44.5	0.7	0.3
Vestige (V)						
Open field (O)						

Sexes in each group approximately equal.

prefer to base our calculations on the summed frequencies of "true patterns" (L, D, W) versus "not true patterns" (L^r, V, O) (Table 27). The logarithms are in Table 28.

For the palmar patterns the same argument is used in a continued calculation of the index. For example, if a true pattern is present in the

TABLE 28. *Ratios of the Frequencies of Mongol/Control Third Interdigital Configurations, Expressed as Logarithms*

CONFIGURATIONS	LEFT	RIGHT
True patterns	+0.15	+0.18
Not true patterns	−0.15	−0.52

left third interdigital area, the "probability" is greater that the subject is a mongol rather than a non-mongol, and the ratio is 54.0:31.3, or 1.7.

PLANTAR CONFIGURATIONS

The most useful of all the dermal configurations are the patterns in the hallucal area of the sole. On nearly half of the left or the right soles

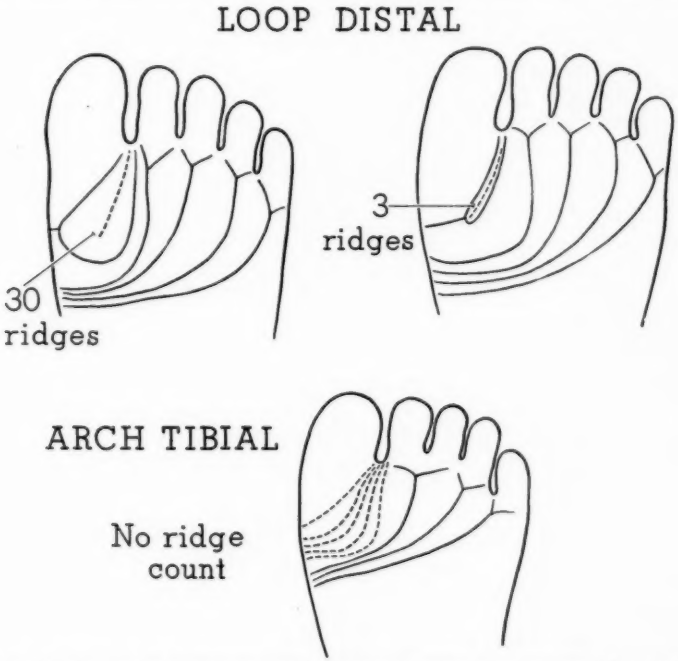

Fig. 54. Outlines of soles of mongoloid imbeciles, showing large and small loop distal hallucal patterns, the latter compared with an arch tibial pattern. (*J. Pediat.*, Vol. 50.)

TABLE 29. *Comparison of Percentage Frequencies of Hallucal Patterns in Mongoloid Imbeciles and Controls*

PATTERNS	PERCENTAGE FREQUENCIES				RATIOS OF MONGOL/CONTROL	
	Left Sole		Right Sole		Left	Right
	Mongols (116)	Controls (300)	Mongols (116)	Controls (300)		
Arch tibial (A^t)	46.6	0.3	47.4	0.3	155.3	158.0
Small loop distal (l^d) (1–20 ridge counts)	33.8	10.0	31.2	13.3	3.4	2.3
Large loop distal (L^d) (21 or more ridge counts)	12.7	41.0	13.6	42.0	0.3	0.3
Vestigial loop distal (V^{ld})	3.4	0.1*	3.4	0.1*	34.0	34.0
Loop tibial (L^t)	2.6	10.0	0.9	9.7	0.2	0.1
Whorl (W)	0.9	33.7	2.6	29.7	0.03	0.1
Tented arch (TA)	0.1*	0.3	0.9	0.1*	0.3	9.0
Arch fibular (A^f)	0.1*	1.4	0.1*	1.7	0.1	0.1
Loop fibular (L^f)	0.1*	0.9	0.1*	1.0	0.1	0.1
Open field/Open field (0/0)	0.1*	3.0	0.1*	2.7	0.03	0.04

* Value assigned for purpose of calculating the index, since the observed frequency was 0.

of mongoloid imbeciles the pattern found is an arch tibial, while in non-mongols this pattern occurs on about one in 300 right or left feet (Table 29).

Conversely, whorls have a low frequency among mongols (left, 0.9; right, 2.6), but a much higher frequency among controls (left, 33.7; right, 29.7).

Loop distal patterns, if considered without regard to size of pattern, show approximately the same frequencies for mongoloids and controls (*left sole*, mongols 46.5 per cent, controls 51.0 per cent; *right sole*, mongols 44.8 per cent, controls 55.3 per cent). However, as a loop

TABLE 30. *Ratios of the Frequencies of Mongol/Control Hallucal Patterns, Expressed as Logarithms*

PATTERNS	LEFT	RIGHT
Arch tibial (A)	+2.19	+2.20
Small loop distal (l^d)	+0.53	+0.36
Large loop distal (L^d)	−0.52	−0.52
Vestigial loop distal (V^{ld})	+1.53	+1.53
Loop tibial (L^t)	−0.70	−1.00
Whorl (W)	−1.52	−1.00
Tented arch (TA)	−0.52	+0.95
Arch fibular (A^f)	−1.00	−1.00
Loop fibular (L^f)	−1.00	−1.00
Open field/Open field (0/0)	−1.52	−1.40

distal pattern becomes smaller it gradually merges into an arch tibial (Fig. 54), and it is these smaller loops which are found more commonly among mongols. The size of the pattern is measured by counting the number of dermal ridges between the core of the pattern and its triradius. When loop distal patterns are divided into *small loops* with 20 or less ridges, and *large loops* with 21 ridges or more, the frequencies of distribution for small loops are as follows:

	LEFT	RIGHT
Mongols	33.8%	31.2%
Controls	10.0%	13.3%

A summary of the frequencies of hallucal patterns, with ratios, is given in Table 29, the logarithms in Table 30.

FINAL CALCULATION OF INDEX

By combining the "probabilities" based on the configurations of these selected digital, palmar and plantar areas, a single score or index is obtained. Example of calculation for a mongol and a university student are given in Tables 31 and 32, accompanied by outline tracings of the dermal configurations of these two subjects (Figs. 55, 56).

TABLE 31. *Calculation of Complete Index for a Mongoloid Imbecile*

	CONFIGURATIONS (See Fig. 4)		LOGARITHMS OF THE RATIOS OF THE CONFIGURATIONS MONGOL/CONTROL		
	Left	Right	Left	Right	From Table
Digital	5—U	1—U	−0.05	+0.09	24
	4—R	2—U	+0.75	+0.42	
	3—U	3—U	+0.07	+0.09	
	2—U	4—U	+0.36	+0.06	
	1—U	5—U	+0.06	−0.05	
Palmar axial triradii	t″	t″	+0.92	+0.80	26
Palmar 3rd interdigital	L	L	+0.23	+0.18	28
Plantar hallucal	A^t	A^t	+2.19	+2.20	30
			+4.03	+3.89	

Total: +8.52
Log. of complete index: +8.5

TABLE 32. *Calculation of Complete Index for a University Student*

	CONFIGURATIONS (See Fig. 5)		LOGARITHMS OF THE RATIOS OF THE CONFIGURATIONS MONGOL/CONTROL		
	Left	Right	Left	Right	From Table
Digital	5—U	1—W	−0.05	−0.17	24
	4—U	2—U	−0.01	+0.42	
	3—U	3—U	+0.07	+0.09	
	2—R	4—U	−0.92	+0.06	
	1—U	5—U	+0.06	−0.05	
Palmar axial triradii	t	t	−0.70	−0.70	26
Palmar 3rd interdigital	0	0	−0.15	−0.52	28
Plantar hallucal	W	W	−1.52	−1.00	30
			−3.22	−1.87	

Total: −5.09
Log. of complete index: −5.1

Finally, the analyses of 200 mongoloid imbeciles and 500 controls are summarized as histograms in Figure 57. The control series comprises mainly university students (sexes approximately equal), although poliomyelitis patients were also included.

There still remains the problem of the overlap between the mongols and controls, and in future calculations we plan to use additional characters such as the presence of a single crease on the fifth digit, the

single simian crease on the palm, and the speckling of the iris. With the addition of these and other characters it is hoped that the overlap will be reduced.

Tests are being conducted for the association of patterns. Also an investigation is in progress to devise a simplified index based upon counts of the number of patterns of certain types present on the left and right hands or the feet of each subject, e.g., the number of whorls in the hallucal area, which might be 0, 1 or 2. Preliminary studies sug-

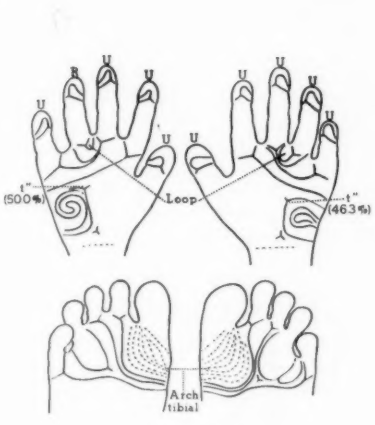

Fig. 55.

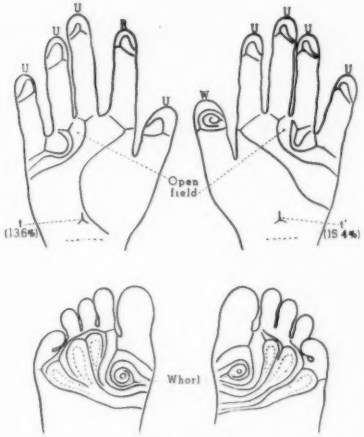

Fig. 56.

Fig. 55. Outlines of the digital, palmar and plantar configurations of a mongoloid imbecile.

Fig. 56. Outlines of the digital, palmar and plantar configurations of a university student.

gest that such an index will distinguish between control and mongol almost as well as the index outlined above.

PRACTICAL APPLICATIONS

The practical applications of these findings are as follows:

1. To supply additional evidence for the diagnosis of mongolism in the newborn infant and to leave on file objective evidence which will never change throughout the life of the individual.

2. To contribute evidence in cases of disagreement regarding the diagnosis of mongolism in the older child.

3. To convince parents that the disturbance of growth in their defective mongoloid child began at least five to six months before birth; that it was not due to any accident of birth or illness in infancy and

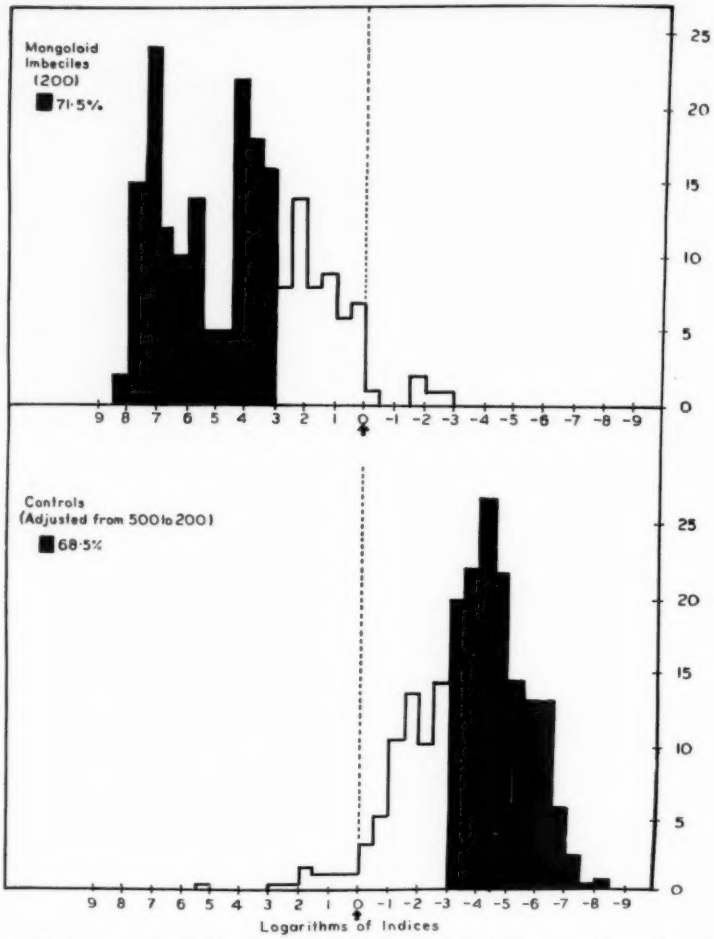

Fig. 57. Histograms of indices based on digital, palmar and plantar patterns of mongoloid imbeciles compared with controls.

that the damage is so extensive that treatment is probably of little avail.

SUMMARY

1. A new method is outlined by which a purely objective diagnosis of mongolism can be made.

2. The method is based on the significant differences between the

frequencies of dermal configurations for mongoloid imbeciles and those of a control series.

3. More than 70 per cent of mongoloid imbeciles possess combinations of patterns not repeated in non-mongols, while more than 68 per cent of the non-mongols have combinations not found among the imbeciles.

4. The dermal configurations used are the finger patterns and certain of the palm and sole patterns.

In this research it is a pleasure to acknowledge the assistance of Prof. D. B. W. Reid (Department of Biometrics) and of Miss Maude Miller (Research Fellow).

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